MICROBIOLOGY



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CHAPTER OVERVIEW

1: Introduction to Microbiology

Microbiology is a broad term which includes virology, mycology, parasitology, bacteriology, immunology, and other branches. A microbiologist is a specialist in microbiology and these related topics. Microbiological procedures usually must be aseptic and use a variety of tools such as light microscopes with a combination of stains and dyes. As microbes are absolutely required for most facets of human life (including the air we breathe and the food we eat) and are potential causes of many human diseases, microbiology is paramount for human society.

1.1: Introduction to Microbiology

1.1A: Defining Microbes

1.1B: History of Microbiology - Hooke, van Leeuwenhoek, and Cohn

1.1C: Pasteur and Spontaneous Generation

1.1D: Koch and Pure Culture

1.2: Microbes and the World

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1.3: The Science of Microbiology

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1.3B Applied Microbiology

1.3C: Immunization, Antiseptics, and Antibiotics

1.3D: Modern Microbiology

Thumbnail: A cluster of Escherichia coli bacteria magnified 10,000 times. (Public Domain; Eric Erbe, digital colorization by Christopher Pooley, both of USDA, ARS, EMU).

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SECTION OVERVIEW

1.1: Introduction to Microbiology

Topic hierarchy

1.1A: Defining Microbes

1.1B: History of Microbiology - Hooke, van Leeuwenhoek, and Cohn

1.1C: Pasteur and Spontaneous Generation

1.1D: Koch and Pure Culture

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1.1A: Defining Microbes

Learning Objectives

- Explain the roles of microorganisms in ecosystems and biotechnology.

A microbe, or microorganism, is a microscopic organism that comprises either a single cell (unicellular); cell clusters; or multicellular, relatively complex organisms. The study of microorganisms is called microbiology, a subject that began with Anton van Leeuwenhoek's discovery of microorganisms in 1675, using a microscope of his own design.

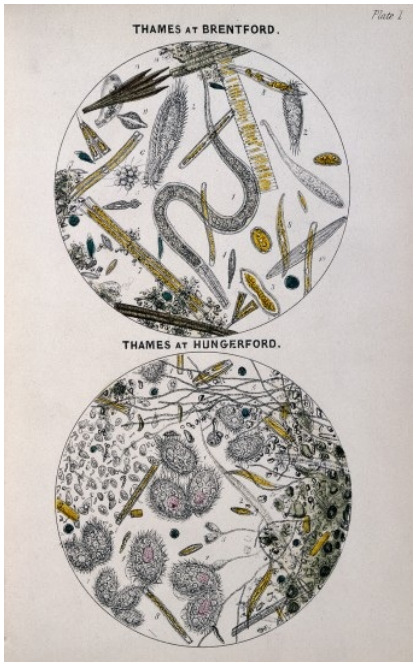

Figure: ***A Drawing of Microbes****: This is a drawing of what Arthur Hill Hassall saw under a microscope in a sample of water taken from the River Thames at two locations. Hassall was able to identify many microscopic organisms not perceptible to the unaided eye,.*

Microorganisms are very diverse; they include bacteria, fungi, algae, and protozoa; microscopic plants (green algae); and animals such as rotifers and planarians. Some microbiologists also include viruses, but others consider these as nonliving. Most microorganisms are unicellular, but this is not universal, since some multicellular organisms are microscopic. Some unicellular protists and bacteria, like *Thiomargarita namibiensis*, are macroscopic and visible to the naked eye.

Microorganisms live in all parts of the biosphere where there is liquid water, including soil, hot springs, on the ocean floor, high in the atmosphere, and deep inside rocks within the Earth's crust. Most importantly, these organisms are vital to humans and the environment, as they participate in the Earth's element cycles, such as the carbon cycle and the nitrogen cycle.

Microorganisms also fulfill other vital roles in virtually all ecosystems, such as recycling other organisms' dead remains and waste products through decomposition. Microbes have an important place in most higher-order multicellular organisms as symbionts, and they are also exploited by people in biotechnology, both in traditional food and beverage preparation, and in modern technologies based on genetic engineering. Pathogenic microbes are harmful, however, since they invade and grow within other organisms, causing diseases that kill humans, animals, and plants.

The Pathogenic Ecology of Microbes

Although many microorganisms are beneficial, many others are the cause of infectious diseases. The organisms involved include pathogenic bacteria, which cause diseases such as plague, tuberculosis, and anthrax. Biofilms —microbial communities that are very difficult to destroy—are considered responsible for diseases like bacterial infections in patients with cystic fibrosis, Legionnaires' disease, and otitis media (middle ear infection). They produce dental plaque; colonize catheters, prostheses, transcutaneous, and orthopedic devices; and infect contact lenses, open wounds, and burned tissue.

Biofilms also produce foodborne diseases because they colonize the surfaces of food and food-processing equipment. Biofilms are a large threat because they are resistant to most of the methods used to control microbial growth. Moreover, the excessive use of antibiotics has resulted in a major global problem since resistant forms of bacteria have been selected over time. A very dangerous strain, methicillin-resistant *Staphylococcus aureus* (MRSA), has wreaked havoc recently.

In addition, protozoans are known to cause diseases such as malaria, sleeping sickness, and toxoplasmosis, while fungi can cause diseases such as ringworm, candidiasis, or histoplasmosis. Other diseases such as influenza, yellow fever, and AIDS are caused by viruses.

Food-borne diseases result from the consumption of contaminated food, pathogenic bacteria, viruses, or parasites that contaminate food. ” Hygiene ” is the avoidance of infection or food spoiling by eliminating microorganisms from the surroundings. As microorganisms (bacteria, in particular) are found virtually everywhere, the levels of harmful microorganisms can be reduced to acceptable levels with proper hygiene techniques. In some cases, however, it is required that an object or substance be completely sterile (i.e., devoid of all living entities and viruses). A good example of this is a hypodermic needle.

Key Points

- While most microbes are unicellular, some multicellular animals and plants are also microscopic and are therefore broadly defined as “microbes.”
- Microbes serve many functions in almost any ecosystem on Earth, including decomposition and nitrogen fixation.
- Many microbes are either pathogens or parasitic organisms, both of which can harm humans.

Key Terms

- **symbiote**: An organism in a partnership with another, such that each profits from the other.
- **pathogenic**: Able to cause a harmful disease.
- **ecosystem**: The interconnectedness of plants, animals, and microbes, not only with each other but also with their environment.

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1.1B: History of Microbiology - Hooke, van Leeuwenhoek, and Cohn

Learning Objectives

- Explain how Van Leeuwenhoek, Spallanzani, Pasteur, Cohn and Koch contributed to the field of microbiology

Pre-microbiology, the possibility that microorganisms existed was discussed for many centuries before their actual discovery in the 17th century. The existence of unseen microbiological life was postulated by Jainism, which is based on Mahavira's teachings as early as 6th century BCE. In his first century book, *On Agriculture*, Roman scholar Marcus Terentius Varro was the first known to suggest the possibility of disease spreading by yet unseen organisms. In his book, he warns against locating a homestead near swamps because "there are bred certain minute creatures that cannot be seen by the eyes, which float in the air and enter the body through the mouth and nose and there cause serious diseases. " In *The Canon of Medicine* (1020), Abū Alī ibn Sīnā (Avicenna) hypothesized that tuberculosis and other diseases might be contagious. In 1546, Girolamo Fracastoro proposed that epidemic diseases were caused by transferable seed-like entities that could transmit infection by direct or indirect contact, or even without contact over long distances. All these early claims about the existence of microorganisms were speculative and were not based on any data or science. Microorganisms were neither proven, observed, nor correctly and accurately described until the 17th century. The reason for this was that all these early studies lacked the microscope.

The Microscope and Discovery of Microorganisms

Antonie van Leeuwenhoek (1632–1723) was one of the first people to observe microorganisms, using a microscope of his own design, and made one of the most important contributions to biology. Robert Hooke was the first to use a microscope to observe living things. Hooke's 1665 book, *Micrographia*, contained descriptions of plant cells. Before Van Leeuwenhoek's discovery of microorganisms in 1675, it had been a mystery why grapes could be turned into wine, milk into cheese, or why food would spoil. Van Leeuwenhoek did not make the connection between these processes and microorganisms, but using a microscope, he did establish that there were forms of life that were not visible to the naked eye. Van Leeuwenhoek's discovery, along with subsequent observations by Spallanzani and Pasteur, ended the long-held belief that life spontaneously appeared from non-living substances during the process of spoilage.



Figure: ***Antoni van Leeuwenhoek****: A drawing of Antoni van Leeuwenhoek, one of the first scientists to use a microscope and identify microbes.*

Lazzaro Spallanzani (1729–1799) found that boiling broth would sterilize it and kill any microorganisms in it. He also found that new microorganisms could settle only in a broth if the broth was exposed to the air.

Louis Pasteur (1822–1895) expanded upon Spallanzani's findings by exposing boiled broths to the air in vessels that contained a filter to prevent all particles from passing through to the growth medium. He also did this in vessels with no filter at all, with air being admitted via a curved tube that prevented dust particles from coming in contact with the broth. By boiling the broth beforehand, Pasteur ensured that no microorganisms survived within the broths at the beginning of his experiment. Nothing grew in the broths in the course of Pasteur's experiment. This meant that the living organisms that grew in such broths came from outside, as spores on dust, rather than spontaneously generated within the broth. Thus, Pasteur dealt the death blow to the theory of spontaneous generation and supported germ theory instead.

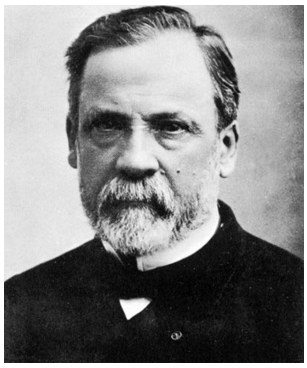

Figure: ***Louis Pasteur****: The famous scientist Louis Pasteur, one of the founders of microbiology.*

Ferdinand Julius Cohn (January 24, 1828 – June 25, 1898) was a German biologist. His classification of bacteria into four groups based on shape (sphericals, short rods, threads, and spirals) is still in use today. Among other things Cohn is remembered for being the first to show that *Bacillus* can change from a vegetative state to an endospore state when subjected to an environment deleterious to the vegetative state. His studies would lay the foundation for the classification of microbes and gave some of the first insights into the incredible complexity and diversity of microbial life.

In 1876, Robert Koch (1843–1910) established that microbes can cause disease. He found that the blood of cattle who were infected with anthrax always had large numbers of *Bacillus anthracis*. Koch found that he could transmit anthrax from one animal to another by taking a small sample of blood from the infected animal and injecting it into a healthy one, and this caused the healthy animal to become sick. He also found that he could grow the bacteria in a nutrient broth, then inject it into a healthy animal, and cause illness. Based on these experiments, he devised criteria for establishing a causal link between a microbe and a disease and these are now known as Koch's postulates. Although these postulates cannot be applied in all cases, they do retain historical importance to the development of scientific thought and are still being used today.

Key Points

- Van Leeuwenhoek is largely credited with the discovery of microbes, while Hooke is credited as the first scientist to describe live processes under a microscope.
- Spallanzani and Pasteur performed several experiments to demonstrate that microbial life does not arise spontaneously.
- Cohn laid the groundwork for discovering and cataloging microbes, while Koch conclusively showed that microbes can cause diseases.

Key Terms

- **classification**: the act of forming into a class or classes; a distribution into groups, as classes, orders, families, etc., according to some common relations or attributes.

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1.1C: Pasteur and Spontaneous Generation

Learning Objectives

- Explain the concept of spontaneous generation

Spontaneous generation is an obsolete body of thought on the ordinary formation of living organisms without descent from similar organisms. Typically, the idea was that certain forms such as fleas could arise from inanimate matter such as dust or that maggots could arise from dead flesh. A variant idea was that of equivocal generation, in which species such as tapeworms arose from unrelated living organisms, now understood to be their hosts.

Doctrines held that these processes were commonplace and regular. Such ideas were in contradiction to that of univocal generation: effectively exclusive reproduction from genetically related parent(s), generally of the same species. The doctrine of spontaneous generation was coherently synthesized by Aristotle, who compiled and expanded the work of prior natural philosophers and the various ancient explanations of the appearance of organisms; it held sway for two millennia.

Today spontaneous generation is generally accepted to have been decisively dispelled during the 19th century by the experiments of Louis Pasteur. He expanded upon the investigations of predecessors, such as Francesco Redi who, in the 17th century, had performed experiments based on the same principles.

Louis Pasteur's 1859 experiment is widely seen as having settled the question. In summary, Pasteur boiled a meat broth in a flask that had a long neck that curved downward, like a goose. The idea was that the bend in the neck prevented falling particles from reaching the broth, while still allowing the free flow of air. The flask remained free of growth for an extended period. When the flask was turned so that particles could fall down the bends, the broth quickly became clouded. In detail, Pasteur exposed boiled broths to air in vessels that contained a filter to prevent all particles from passing through to the growth medium, and even in vessels with no filter at all, with air being admitted via a long tortuous tube that would not allow dust particles to pass. Nothing grew in the broths unless the flasks were broken open, showing that the living organisms that grew in such broths came from outside, as spores on dust, rather than spontaneously generated within the broth. This was one of the last and most important experiments disproving the theory of spontaneous generation.

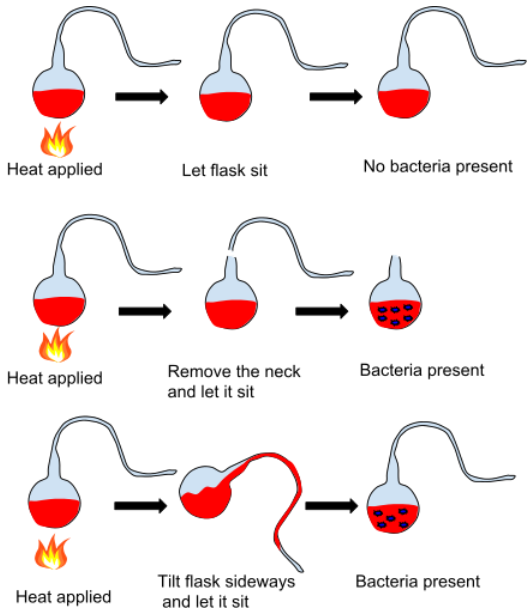

Figure: ***Pasteur's test of spontaneous generation****: By sterilizing a food source and keeping it isolated from the outside, Pasteur observed no putrefaction of the food source (top panel). Upon exposure to the outside environment, Pasteur observed the putrefaction of the food source (bottom panel). This strongly suggested that the components needed to create life do not spontaneously arise. Louis Pasteur's pasteurization experiment illustrates the fact that the spoilage of liquid was caused by particles in the air rather than the air itself. These experiments were important pieces of evidence supporting the idea of germ theory of disease. (CC BY-SA 4.0; Kgerow16).*

Despite his experiment, objections from persons holding the traditional views persisted. Many of these residual objections were routed by the work of John Tyndall, succeeding the work of Pasteur. Ultimately, the ideas of spontaneous generation were displaced

by advances in germ theory and cell theory. Disproof of the traditional ideas of spontaneous generation is no longer controversial among professional biologists. Objections and doubts have been dispelled by studies and documentation of the life cycles of various life forms. However, the principles of the very different matter of the original abiogenesis on this planet — of living from nonliving material — are still under investigation

Key Points

- Before the discovery of microbes, it was widely thought that life, as in the case of rotting food, arose from nothing. This idea was referred to as spontaneous generation.
- By sterilizing cultures and keeping them isolated from the open air, Pasteur found that contamination of the media only occurred upon exposure to the outside environment, showing that some element was needed to give rise to life. In other words, life does not arise spontaneously.
- Despite Pasteur's work and the work of others, it still took a better understanding of germ theory and cell theory to finally displace the concept of spontaneous generation.

Key Terms

- **abiogenesis**: The origination of living organisms from lifeless matter; such genesis as does not involve the action of living parents; spontaneous generation.
- **germ theory**: The germ theory of disease, also called the pathogenic theory of medicine, is a theory that proposes that microorganisms are the cause of many diseases. Although highly controversial when first proposed, germ theory was validated in the late 19th century and is now a fundamental part of modern medicine and clinical microbiology, leading to such important innovations as antibiotics and hygienic practices.

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1.1D: Koch and Pure Culture

Learning Objectives

- Explain Robert Koch's postulates

Robert Koch was born in Clausthal in the Harz Mountains, then part of the Kingdom of Hanover, as the son of a mining official. He studied medicine at the University of Göttingen and graduated in 1866. He then served in the Franco-Prussian War and later became district medical officer in Wollstein (Wolsztyn), Prussian Poland. Working with very limited resources, he became one of the founders of bacteriology, the other major figure being Louis Pasteur.

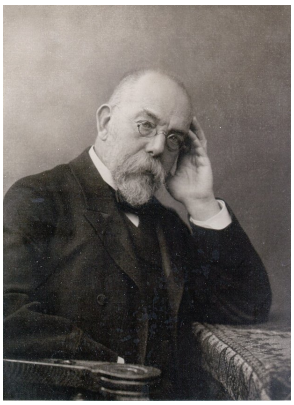

Figure: ***Robert Koch****: An image of Robert Koch, a pioneering microbiologist. Koch's research and methods helped link the causal nature of microbes to certain diseases, including anthrax.*

After Casimir Davaine demonstrated the direct transmission of the anthrax bacillus between cows, Koch studied anthrax more closely. He invented methods to purify the bacillus from blood samples and grow pure cultures. He found that, while it could not survive outside a host for long, anthrax built persisting endospores that could last a long time. These endospores, embedded in soil, were the cause of unexplained "spontaneous" outbreaks of anthrax. Koch published his findings in 1876 and was rewarded with a job at the Imperial Health Office in Berlin in 1880. In 1881, he urged for the sterilization of surgical instruments using heat.

Probably as important as his work on tuberculosis, for which he was awarded a Nobel Prize in 1905, are Koch's postulates. These postulates stated that to establish that an organism is the cause of a disease, it must be found in all cases of the disease examined. Additionally, it must be absent in healthy organisms prepared and maintained in a pure culture capable of producing the original infection, even after several generations in culture retrievable from an inoculated animal and cultured again. By using his methods, Koch's pupils found the organisms responsible for diphtheria, typhoid, pneumonia, gonorrhoea, cerebrospinal meningitis, leprosy, bubonic plague, tetanus, and syphilis.

Perhaps the key method Koch developed was the ability to isolate pure cultures, explained in brief here. Pure cultures of multicellular organisms are often more easily isolated by simply picking out a single individual to initiate a culture. This is a useful technique for pure culture of fungi, multicellular algae, and small metazoa. Developing pure culture techniques is crucial to the observation of the specimen in question. The most common method to isolate individual microbes and produce a pure culture is to prepare a streak plate. The streak plate method is a way to physically separate the microbial population and is done by spreading the inoculate back and forth with an inoculating loop over the solid agar plate. Upon incubation, colonies will arise and single cells will have been isolated from the biomass.

Key Points

- Koch's research and methods helped link the causal nature of microbes to certain diseases, such as anthrax.
- As developed by Koch, pure cultures allow the pure isolation of a microbe, which is vital in understanding how an individual microbe may contribute to a disease.
- According to Koch's postulates, for an organism to be the cause of a disease, it must be found in all cases of the disease and must be absent from healthy organisms, as well as maintained in pure culture capable of producing the original infection.

Key Terms

- **anthrax**: An infectious bacterial disease of herbivores than can also occur in humans through contact with infected animals, tissue from infected animals, or high concentrations of anthrax spores.
- **metazoa**: All those multicellular animals, of the subkingdom Metazoa, that have differentiated tissue.
- **tuberculosis**: An infectious disease of humans and animals caused by a species of mycobacterium mainly infecting the lungs where it causes tubercles characterized by the expectoration of mucus and sputum, fever, weight loss, and chest pain, and transmitted through inhalation or ingestion of bacteria.

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SECTION OVERVIEW

1.2: Microbes and the World

Topic hierarchy

1.2A Types of Microorganisms

1.2B: Classification of Microorganisms

1.2C: Microbes and the Origin of Life on Earth

1.2D: Environmental Diversity of Microbes

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1.2A Types of Microorganisms

Microorganisms make up a large part of the planet's living material and play a major role in maintaining the Earth's ecosystem.

Learning Objectives

- Define the differences between microbial organisms.

Key Points

- Microorganisms are divided into seven types: bacteria, archaea, protozoa, algae, fungi, viruses, and multicellular animal parasites (helminths).
- Each type has a characteristic cellular composition, morphology, mean of locomotion, and reproduction.
- Microorganisms are beneficial in producing oxygen, decomposing organic material, providing nutrients for plants, and maintaining human health, but some can be pathogenic and cause diseases in plants and humans.

Key Terms

- **Gram stain**: A method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative).
- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.

Microorganisms or microbes are microscopic organisms that exist as unicellular, multicellular, or cell clusters. Microorganims are widespread in nature and are beneficial to life, but some can cause serious harm. They can be divided into six major types: bacteria, archaea, fungi, protozoa, algae, and viruses.

Bacteria

Bacteria are unicellular organisms. The cells are described as prokaryotic because they lack a nucleus. They exist in four major shapes: bacillus (rod shape), coccus (spherical shape), spirilla (spiral shape), and vibrio (curved shape). Most bacteria have a peptidoglycan cell wall; they divide by binary fission; and they may possess flagella for motility. The difference in their cell wall structure is a major feature used in classifying these organisms.

According to the way their cell wall structure stains, bacteria can be classified as either Gram-positive or Gram-negative when using the Gram staining. Bacteria can be further divided based on their response to gaseous oxygen into the following groups: aerobic (living in the presence of oxygen), anaerobic (living without oxygen), and facultative anaerobes (can live in both environments).

According to the way they obtain energy, bacteria are classified as heterotrophs or autotrophs. Autotrophs make their own food by using the energy of sunlight or chemical reactions, in which case they are called chemoautotrophs. Heterotrophs obtain their energy by consuming other organisms. Bacteria that use decaying life forms as a source of energy are called saprophytes.

Archaea

Archaea or Archaebacteria differ from true bacteria in their cell wall structure and lack peptidoglycans. They are prokaryotic cells with avidity to extreme environmental conditions. Based on their habitat, all Archaeans can be divided into the following groups: methanogens (methane-producing organisms), halophiles (archaeans that live in salty environments), thermophiles (archaeans that live at extremely hot temperatures), and psychrophiles (cold-temperature Archaeans). Archaeans use different energy sources like hydrogen gas, carbon dioxide, and sulphur. Some of them use sunlight to make energy, but not the same way plants do. They absorb sunlight using their membrane pigment, bacteriorhodopsin. This reacts with light, leading to the formation of the energy molecule adenosine triphosphate (ATP).

Fungi

Fungi (mushroom, molds, and yeasts) are eukaryotic cells (with a true nucleus). Most fungi are multicellular and their cell wall is composed of chitin. They obtain nutrients by absorbing organic material from their environment (decomposers), through symbiotic relationships with plants (symbionts), or harmful relationships with a host (parasites). They form characteristic filamentous tubes called hyphae that help absorb material. The collection of hyphae is called mycelium. Fungi reproduce by releasing spores.

Protozoa

Protozoa are unicellular aerobic eukaryotes. They have a nucleus, complex organelles, and obtain nourishment by absorption or ingestion through specialized structures. They make up the largest group of organisms in the world in terms of numbers, biomass, and diversity. Their cell walls are made up of cellulose. Protozoa have been traditionally divided based on their mode of locomotion: flagellates produce their own food and use their whip-like structure to propel forward, ciliates have tiny hair that beat to produce movement, amoeboids have false feet or pseudopodia used for feeding and locomotion, and sporozoans are non-motile. They also have different means of nutrition, which groups them as autotrophs or heterotrophs.

Algae

Algae, also called cyanobacteria or blue-green algae, are unicellular or multicellular eukaryotes that obtain nourishment by photosynthesis. They live in water, damp soil, and rocks and produce oxygen and carbohydrates used by other organisms. It is believed that cyanobacteria are the origins of green land plants.

Viruses

Viruses are noncellular entities that consist of a nucleic acid core (DNA or RNA) surrounded by a protein coat. Although viruses are classified as microorganisms, they are not considered living organisms. Viruses cannot reproduce outside a host cell and cannot metabolize on their own. Viruses often infest prokaryotic and eukaryotic cells causing diseases.

Multicellular Animal Parasites

A group of eukaryotic organisms consisting of the flatworms and roundworms, which are collectively referred to as the helminths. Although they are not microorganisms by definition, since they are large enough to be easily seen with the naked eye, they live a part of their life cycle in microscopic form. Since the parasitic helminths are of clinical importance, they are often discussed along with the other groups of microbes.

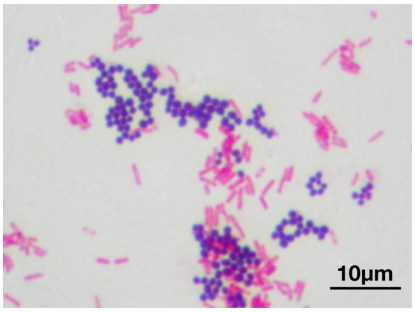

Figure: **Gram Stain**: This is a microscopic image of a Gram stain of mixed Gram-positive cocci (Staphylococcus aureus, purple) and Gram-negative bacilli (Escherichia coli, red).

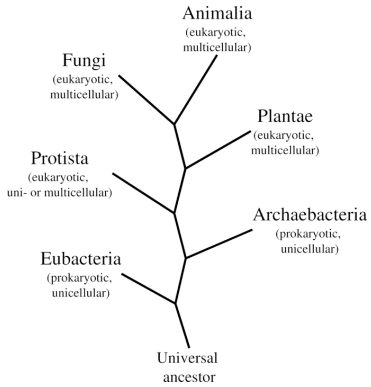

Figure: **Types of microorganisms**: This tree of life shows the different types of microorganisms.

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1.2B: Classification of Microorganisms

Microorganisms are classified into taxonomic categories to facilitate research and communication.

Learning Objectives

- Assess how early life changed the earth

Key Points

- The classification system is constantly changing with the advancement of technology.
- The most recent classification system includes five kingdoms that are further split into phylum, class, order, family, genus, and species.
- Microorganisms are assigned a scientific name using binomial nomenclature.

Key Terms

- **DNA fingerprinting**: A method of isolating and mapping sequences of a cell's DNA to identify it.

Life on Earth is famous for its diversity. Throughout the world we can find many millions of different forms of life. Biologic classification helps identify each form according to common properties (similarities) using a set of rules and an estimate as to how closely related it is to a common ancestor (evolutionary relationship) in a way to create an order. By learning to recognize certain patterns and classify them into specific groups, biologists are better able to understand the relationships that exist among a variety of living forms that inhabit the planet.

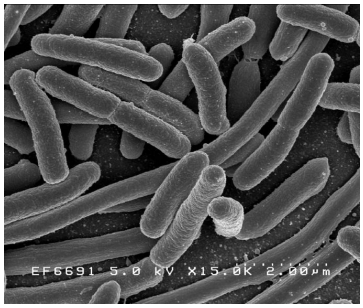

Figure: **Classification of E. coli**: Domain: Bacteria, Kingdom: Eubacteria, Phylum: Proteobacteria, Class: Gammaproteobacteria, Order: Enterobacteriales, Family: Enterobacteriaceae, Genus: Escherichia, Species: E. coli.

The first, largest, and most inclusive group under which organisms are classified is called a domain and has three subgroups: bacteria, archae, and eukarya. This first group defines whether an organism is a prokaryote or a eukaryote. The domain was proposed by the microbiologist and physicist Carl Woese in 1978 and is based on identifying similarities in ribosomal RNA sequences of microorganisms.

The second largest group is called a kingdom. Five major kingdoms have been described and include prokaryota (e.g. archae and bacteria), protoctista (e.g. protozoa and algae), fungi, plantae, and animalia. A kingdom is further split into phylum or division, class, order, family, genus, and species, which is the smallest group.

The science of classifying organisms is called taxonomy and the groups making up the classification hierarchy are called taxa. Taxonomy consists of classifying new organisms or reclassifying existing ones. Microorganisms are scientifically recognized using a binomial nomenclature using two words that refer to the genus and the species. The names assigned to microorganisms are in Latin. The first letter of the genus name is always capitalized. Classification of microorganisms has been largely aided by studies of fossils and recently by DNA sequencing. Methods of classifications are constantly changing. The most widely employed methods for classifying microbes are morphological characteristics, differential staining, biochemical testing, DNA fingerprinting or DNA base composition, polymerase chain reaction, and DNA chips.

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1.2C: Microbes and the Origin of Life on Earth

Life on Earth is thought to have originated from the oldest single-cell archaea and bacteria.

Learning Objectives

- Assess the characteristics of pre-life earth and which adaptations allowed early microbial life to flourish.

Key Points

- The proposed mechanisms for the origin of life on Earth include endosymbiosis and panspermia. Both are debatable theories.
- In these two theories, bacteria and extremophile archaea are thought to have initiated an oxygenated atmosphere creating new forms of life.
- Evolutionary processes over billions of years gave rise to the biodiversity of life on Earth.

Key Terms

- **endosymbiosis**: A condition of living within the body or cells of another organism.
- **panspermia**: The hypothesis that microorganisms may transmit life from outer space to habitable bodies; or the process of such transmission.

Scientific evidence suggests that life began on Earth some 3.5 billion years ago. Since then, life has evolved into a wide variety of forms, which biologists have classified into a hierarchy of taxa. Some of the oldest cells on Earth are single-cell organisms called archaea and bacteria. Fossil records indicate that mounds of bacteria once covered young Earth. Some began making their own food using carbon dioxide in the atmosphere and energy they harvested from the sun. This process (called photosynthesis) produced enough oxygen to change Earth's atmosphere.

Soon afterward, new oxygen-breathing life forms came onto the scene. With a population of increasingly diverse bacterial life, the stage was set for more life to form. There is compelling evidence that mitochondria and chloroplasts were once primitive bacterial cells. This evidence is described in the endosymbiotic theory. Symbiosis occurs when two different species benefit from living and working together. When one organism actually lives inside the other it's called endosymbiosis. The endosymbiotic theory describes how a large host cell and ingested bacteria could easily become dependent on one another for survival, resulting in a permanent relationship.

Over millions of years of evolution, mitochondria and chloroplasts have become more specialized and today they cannot live outside the cell. Mitochondria and chloroplasts have striking similarities to bacteria cells. They have their own DNA, which is separate from the DNA found in the nucleus of the cell. And both organelles use their DNA to produce many proteins and enzymes required for their function. A double membrane surrounding both mitochondria and chloroplasts is further evidence that each was ingested by a primitive host. The two organelles also reproduce like bacteria, replicating their own DNA and directing their own division.

Mitochondrial DNA (mtDNA) has a unique pattern of inheritance. It is passed down directly from mother to child, and it accumulates changes much more slowly than other types of DNA. Because of its unique characteristics, mtDNA has provided important clues about evolutionary history. For example, differences in mtDNA are examined to estimate how closely related one species is to another.



Figure: **Extremophiles**: Photosynthetic fossilized cyanobacteria in a billion year old rock formation of Glacier National Park, Montana, USA.

Conditions on Earth 4 billion years ago were very different than they are today. The atmosphere lacked oxygen, and an ozone layer did not yet protect Earth from harmful radiation. Heavy rains, lightning, and volcanic activity were common. Yet the earliest cells originated in this extreme environment. Extremophiles archaea still thrive in extreme habitats. Astrobiologists are now using archaea to study the origins of life on Earth and other planets. Because archaea inhabit places previously considered incompatible with life, they may provide clues that will improve our ability to detect extraterrestrial life. Interestingly, current research suggests archaea may be capable of space travel by meteorite. Such an event termed panspermia could have seeded life on Earth or elsewhere.

The presence of archaea and bacteria changed Earth dramatically. They helped establish a stable atmosphere and produced oxygen in such quantities that eventually life forms could evolve that needed oxygen. The new atmospheric conditions calmed the weather so that the extremes were less severe. Life had created the conditions for new life to be formed. This process is one of the great wonders of nature.

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1.2D: Environmental Diversity of Microbes

Learning Objectives

- Summarize how microbial diversity contributes to microbial occupation of diverse geographical niches.

The microbial world encompasses most of the phylogenetic diversity on Earth, as all Bacteria, all Archaea, and most lineages of the Eukarya are microorganisms. Microbes live in every kind of habitat (terrestrial, aquatic, atmospheric, or living host) and their presence invariably affects the environment in which they grow. Their diversity enables them to thrive in extremely cold or extremely hot environments. Their diversity also makes them tolerant of many other conditions, such as limited water availability, high salt content, and low oxygen levels.

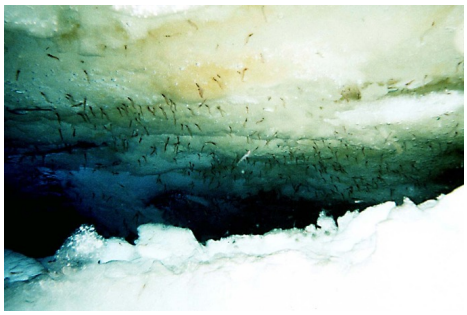

Figure: **Microorganisms in a cold environment**: Ice algae in Antartica.



Figure: **Microorganisms in a hot environment**: Algae growing in a hot pool in New Zealand.

Not every microbe can survive in all habitats, though. Each type of microbe has evolved to live within a narrow range of conditions. Although the vast majority of microbial diversity remains undetermined, it is globally understood that the effects of microorganisms on their environment can be beneficial. The beneficial effects of microbes derive from their metabolic activities in the environment, their associations with plants and animals, and from their use in food production and biotechnological processes.

In turn, the environment and the recent temperature anomalies play a crucial role in driving changes to the microbial communities. For instance, the assemblage of microbes that exists on the surface of seawater is thought to have undergone tremendous change with respect to composition, abundance, diversity, and virulence as a result of climate-driving sea surface warming.

For microbiologists, it is critical to study microbial adaptation to different environments and their function in those environments to understand global microbial diversity, ecology, and evolution. They rely on specific physical and chemical factors such as measuring temperature, pH, and salinity within a certain geography to formulate a comparison among microbial communities and the environment different species can tolerate. Researchers collect samples from geographical areas with different environmental conditions and between seasons to determine how dispersal patterns shape microbial communities and understand why organisms live where they do. As such, microbial communities from coastal and open oceans, polar regions, rivers, lakes, soils, atmosphere, and the human body can be tested. These samplings create a starting point to understand how the abundance and composition of microbial communities correlate with climatic perturbations, interact to effect ecosystem processes, and influence human health. Interfering with natural microbial biomass disrupts the balance of nature and the ecosystem and leads to loss of biodiversity.

Key Points

- Different microbial species thrive under different environmental conditions.
- Microbial communities occupy aquatic and terrestrial habitats and constitute the majority of biodiversity on Earth.
- Microbial diversities sustain the ecosystem in which they grow.

Key Terms

- **biodiversity**: The diversity (number and variety of species) of plant and animal life within a region.
- **biomass**: The total mass of all living things within a specific area or habitat.

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SECTION OVERVIEW

1.3: The Science of Microbiology

Topic hierarchy

1.3A: Basic Microbiology

1.3B Applied Microbiology

1.3C: Immunization, Antiseptics, and Antibiotics

1.3D: Modern Microbiology

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1.3A: Basic Microbiology

Microbiology is the study of microscopic organisms and how they interact with humans and the environment.

Learning Objectives

- Evaluate the science of basic microbiology; understand the fundamental aspects of microbiology.

Key Points

- Microbiology focuses on organisms that are very small using various tools, which is a process done by microbiologists.
- As microbes are essential for human life and as microbes can cause human diseases, microbiology is therefore very important.
- The numbers of individual microbes and the number of microbes in and on the earth is staggering in proportions.

Key Terms

- **quantitation**: The process of quantitating.
- **immunology**: The branch of medicine that studies the body's immune system.
- **culturable**: Able to be cultured (grown in a suitable environment).

Microbiology is the study of microscopic organisms (microbes), which are defined as any living organism that is either a single cell (unicellular), a cell cluster, or has no cells at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

Microbiology typically includes the study of the immune system, or immunology. Generally, immune systems interact with pathogenic microbes; these two disciplines often intersect which is why many colleges offer a paired degree such as "Microbiology and Immunology. "



Figure: **Microbiologist**: A microbiology officer aboard a US naval ship examines wound cultures in the ship's microbiology laboratory.

Microbiology is a broad term which includes virology, mycology, parasitology, bacteriology, immunology, and other branches. A microbiologist is a specialist in microbiology and these related topics. Microbiological procedures usually must be aseptic and use a variety of tools such as light microscopes with a combination of stains and dyes. As microbes are absolutely required for most facets of human life (including the air we breathe and the food we eat) and are potential causes of many human diseases, microbiology is paramount for human society.

Research in the microbiology field is expanding, and in the coming years, we should see the demand for microbiologists in the workforce increase. It is estimated that only about one percent of the microorganisms present in a given environmental sample are culturable and the number of bacterial cells and species on Earth is still not possible to be determined. Recent estimates indicate that this number might be extremely high at five to the power of thirty. Although microbes were directly observed over three hundred years ago, the precise determination, quantitation, and description of its functions is far from complete, given the overwhelming diversity detected by genetic and culture-independent means.

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1.3B Applied Microbiology

The information gained by microbiologists can be applied to many medicinal and commercial endeavors.

Learning Objectives

- Explain applied microbiology

Key Points

- Using knowledge gained by microbiologists studying microbes, several fields of applied microbiology have formed.
- While food and medicinal applications are a big portion of applied microbiology, the study of microbes has lead to entire commercial industries which affect almost all aspects of human life.
- There are a myriad of practical applications that microbiology contributes to, including several parts of food production and medicinal applications.

Key Terms

- **rhizosphere**: The soil region subject to the influence of plant roots and their associated microorganisms.
- **biotechnology**: The use of living organisms (especially microorganisms) in industrial, agricultural, medical, and other technological applications.
- **pathogenic**: Able to cause harmful disease.

Microbiology is the study of microbes, which affect almost every aspect of life on the earth. In addition, there are huge commercial and medicinal benefits in understanding microbes. The application of this understanding is known as applied microbiology. There are many different types of applied microbiology which can be briefly defined as follows:

Medical Microbiology

Medical microbiology is the study of the pathogenic microbes and the role of microbes in human illness. This includes the study of microbial pathogenesis and epidemiology and is related to the study of disease pathology and immunology.

Pharmaceutical Microbiology

The study of microorganisms that are related to the production of antibiotics, enzymes, vitamins, vaccines, and other pharmaceutical products. Pharmaceutical microbiology also studies the causes of pharmaceutical contamination and spoil.

Industrial Microbiology

The exploitation of microbes for use in industrial processes. Examples include industrial fermentation and waste-water treatment. Closely linked to the biotechnology industry. This field also includes brewing, an important application of microbiology.

Microbial Biotechnology

The manipulation of microorganisms at the genetic and molecular level to generate useful products.

Food Microbiology and Dairy Microbiology

The study of microorganisms causing food spoilage and food-borne illness. Microorganisms can produce foods, for example by fermentation.



Figure: **Applied microbiology – Fermentation**: One of the oldest and well-known examples of applied microbiology is fermentation. In this picture the large tanks are being used for the fermentation of grapes to make wine.

Agricultural Microbiology

The study of agriculturally relevant microorganisms. This field can be further classified into the following subfields:

- Plant microbiology and plant pathology – The study of the interactions between microorganisms and plants and plant pathogens.
- Soil microbiology – The study of those microorganisms that are found in soil.
- Veterinary microbiology – The study of the role in microbes in veterinary medicine or animal taxonomy.
- Environmental microbiology – The study of the function and diversity of microbes in their natural environments. This involves the characterization of key bacterial habitats such as the rhizosphere and phyllosphere, soil and groundwater ecosystems, open oceans or extreme environments (extremophiles). This field includes other branches of microbiology such as: microbial ecology (microbially-mediated nutrient cycling), geomicrobiology, (microbial diversity), water microbiology (the study of those microorganisms that are found in water), aeromicrobiology (the study of airborne microorganisms) and epidemiology (the study of the incidence, spread, and control of disease).

This is by no means an exhaustive list of the different types of applied microbiology, but gives an indication of the expansive variety of the field and some of the benefits these studies entail.

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1.3C: Immunization, Antiseptics, and Antibiotics

Understanding microbes gives us the ability to fight pathogens using immunization, antiseptics, and antibiotics.

Learning Objectives

- Compare immunization, antiseptics and antibiotics, and how they are used to combat human pathogens

Key Points

- Immunization is the fortification of our own immune system, priming it against potential future infections by specific microbes.
- Antiseptics are broadly defined as substances we can use on our body or surfaces around us to slow or kill microbes that could potentially harm us.
- Antibiotics, like antiseptics, can slow or kill microbes. However, unlike antiseptics, antibiotics can circulate in the human blood system and be used to fight microbial infections.

Key Terms

- **anaphylactic shock**: A severe and rapid systemic allergic reaction to an allergen, constricting the trachea and preventing breathing.
- **immunogen**: any substance that elicits a immune response; an antigen

Surprisingly, most microbes are not harmful to humans. In fact, they are all around us and even a part of us. However, some microbes are human pathogens; to combat these, we use immunization, antiseptics, and antibiotics.

Immunization is the process by which an individual's immune system becomes fortified against an agent (known as the immunogen).



Figure: **Flu Immunization**: A naval officer self-administers a nasal spray that immunizes him against the flu.

When the immune system is exposed to molecules that are foreign to the body, it will orchestrate an immune response. It will also develop the ability to respond quickly to subsequent encounters with the same substance, a phenomenon known as immunological memory. Therefore, by exposing a person to an immunogen in a controlled way, the body can learn to protect itself: this is called active immunization.

Vaccines against microorganisms that cause diseases can prepare the body's immune system, thus helping it fight or prevent an infection. The most important elements of the immune system that are improved by immunization are the T cells, the B cells, and the antibodies B cells produce. Memory B cells and memory T cells are responsible for the swift response to a second encounter with a foreign molecule. Through the use of immunizations, some infections and diseases have been almost completely eradicated throughout the United States and the world. For example, polio was eliminated in the U.S. in 1979. Active immunization and vaccination has been named one of the "Ten Great Public Health Achievements in the 20th Century. "

By contrast, in *passive* immunization, pre-synthesized elements of the immune system are transferred to a human body so it does not need to produce these elements itself. Currently, antibodies can be used for passive immunization. This method of immunization starts to work very quickly; however, it is short-lasting because the antibodies are naturally broken down and will disappear altogether if there are no B cells to produce more of them. Passive immunization occurs physiologically, when antibodies are transferred from mother to fetus during pregnancy, to protect the fetus before and shortly after birth. The antibodies can be produced in animals, called " serum therapy," although there is a high chance of anaphylactic shock because of immunity against animal serum itself. Thus, humanized antibodies produced *in vitro* by cell culture are used instead if available.

In early inquiries before there was an understanding of microbes, much emphasis was given to the prevention of putrefaction. Procedures were carried out to determine the amount of agent that needed to be added to a given solution in order to prevent the development of pus and putrefaction. However, due to a lack of understanding of germ theory, this method was inaccurate. Today, an antiseptic is judged by its effect on pure cultures of a defined microbe or on their vegetative and spore forms.

Antiseptics are antimicrobial substances that are applied to living tissue to reduce the possibility of infection, sepsis, or putrefaction. Their earliest known systematic use was in the ancient practice of embalming the dead. Antiseptics are generally distinguished from antibiotics by the latter's ability to be transported through the lymphatic system to destroy bacteria within the body, and from disinfectants, which destroy microorganisms found on non-living objects. Some antiseptics are true germicides, capable of destroying microbes (bacteriocidal), while others are bacteriostatic and only prevent or inhibit bacterial growth. Microbicides that destroy virus particles are called viricides or antivirals.

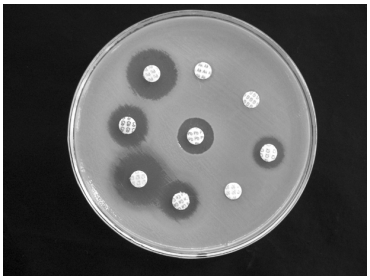

Figure: **Antibiotic Testing**: Discs soaked with various compounds are put onto a lawn of bacteria. If the compound on the disc kills or slows bacteria growth, a "halo" of clear media is seen.

An antibacterial is a compound or substance that kills or slows down the growth of bacteria. The term is often used synonymously with the term antibiotic; today, however, with increased knowledge of the causative agents of various infectious diseases, the term "antibiotic" has come to denote a broader range of antimicrobial compounds, including anti-fungal and other compounds.

The word "antibiotic" was first used in 1942 by Selman Waksman and his collaborators to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This definition excluded substances that kill bacteria but are not produced by microorganisms (such as gastric juices and hydrogen peroxide). It also excluded synthetic antibacterial compounds, such as the sulfonamides. Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 amu. With advances in medicinal chemistry, most of today's antibacterials are semisynthetic modifications of various natural compounds.

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1.3D: Modern Microbiology

Learning Objectives

- Discuss the fundamental aspects of microbiology

Modern microbiolgy began with the discovery of microbes, and the scope and scale of the field continues to expand today. While there is some debate, modern microbiology is accepted by most to begin with observations by the Dutch draper and haberdasher, Antonie van Leeuwenhoek, who lived for most of his life in Delft, Holland. In 1676, van Leeuwenhoek observed bacteria and other microorganisms, using a single-lens microscope of his own design. While van Leeuwenhoek is often cited as the first to observe microbes, Robert Hooke made the first recorded microscopic observation, of the fruiting bodies of molds, in 1665.

It has been suggested that a Jesuit priest called Athanasius Kircher was the first to observe microorganisms. One of his books contains a chapter in Latin, which reads in translation – "Concerning the wonderful structure of things in nature, investigated by Microscope." Here, he wrote "who would believe that vinegar and milk abound with an innumerable multitude of worms. " He noted that putrid material is full of innumerable creeping animalcule. These observations antedate Robert Hooke's Micrographia by nearly 20 years and were published some 29 years before van Leeuwenhoek saw protozoa.



Figure: ***Athanasius Kirche****: A portrait of the 17th century Jesuit priest Athanasius Kirche, who arguably discovered microbes.*

The field of bacteriology (later a subdiscipline of microbiology) was founded in the 19th century by Ferdinand Cohn, a botanist whose studies on algae and photosynthetic bacteria led him to describe several bacteria including Bacillus and Beggiatoa. Cohn was also the first to formulate a scheme for the taxonomic classification of bacteria and discover spores. Louis Pasteur and Robert Koch were contemporaries of Cohn's and are often considered to be the father of microbiology and medical microbiology, respectively. Pasteur is most famous for his series of experiments designed to disprove the then widely held theory of spontaneous generation, thereby solidifying microbiology's identity as a biological science. Pasteur also designed methods for food preservation (pasteurization) and vaccines against several diseases such as anthrax, fowl cholera, and rabies.

Koch is best known for his contributions to the germ theory of disease, proving that specific diseases were caused by specific pathogenic microorganisms. He developed a series of criteria that have become known as the Koch's postulates. Koch was one of the first scientists to focus on the isolation of bacteria in pure culture resulting in his description of several novel bacteria including *Mycobacterium tuberculosis*, the causative agent of tuberculosis. While Pasteur and Koch are often considered the founders of microbiology, their work did not accurately reflect the true diversity of the microbial world because of their exclusive focus on microorganisms having direct medical relevance.

It was not until the late 19th century and the work of Martinus Beijerinck and Sergei Winogradsky, the founders of general microbiology (an older term encompassing aspects of microbial physiology, diversity, and ecology), that the true breadth of microbiology was revealed. Beijerinck made two major contributions to microbiology: the discovery of viruses and the development of enrichment culture techniques. While his work on the tobacco mosaic virus (TMV) established the basic principles

of virology, it was his development of enrichment culturing that had the most immediate impact on microbiology by allowing for the cultivation of a wide range of microbes with wildly different physiologies. Winogradsky was the first to develop the concept of chemoautotrophy and to thereby reveal the essential role microorganisms played in geochemical processes. Specifically, he was responsible for the first isolation and description of both nitrifying and nitrogen-fixing bacteria.



Figure: ***Sergei Winogradsky****: An image of Sergei Winogradsky,who discovered nitrogen-fixing bacteria.*

Key Points

- There is some debate as to who was exactly first, but Antonie van Leeuwenhoek, Athanasius Kircher, and Robert Hooke were the first people to view microbes using some of the first self-built microscopes.
- Ferdinand Cohn, Louis Pasteur, and Robert Koch were pioneers in bacteriology, the discovery and understanding of the subset of microbes that are bacteria. This had a direct and immediate impact on food storage and disease causality.
- Martinus Beijerinck and Sergei Winogradsky are credited with the discovery of general microbiology, which laid the ground work for our understanding of microbial physiology, diversity, and ecology.

Key Terms

- **chemoautotrophy**: When a simple organism, such as a protozoan, derives its energy from chemical processes rather than photosynthesis.
- **pasteurization**: heat-treatment of a perishable food to destroy heat-sensitive vegetative cells followed by immediate cooling to limit growth of the surviving cells and germination of spores
- **rabies**: a viral disease that causes acute encephalitis in warm-blooded animals and people, characterised by abnormal behaviour such as excitement, aggressiveness, and dementia, followed by paralysis and death
- **animalcule**: An older term for a minute or microscopic animal or protozoan.

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CHAPTER OVERVIEW

10: Epidemiology

Epidemiology is the study of the patterns, causes, and effects of health and disease conditions in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results. Epidemiology has helped develop methodology used in clinical research, public health studies and, to a lesser extent, basic research in the biological sciences.

10.1: Principles of Epidemiology

10.1A: History of Epidemiology

10.1B: The Science of Epidemiology

10.1C: The Vocabulary Epidemiology

10.1D: Koch's Postulates

10.1E: Exceptions to Koch's Postulates

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10.2B: Disease Severity and Duration

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10.5H: Technology and New Infectious Agents

10.5I: Current Epidemics

Thumbnail: Mary Mallon, better known as Typhoid Mary, was the first person in the United States identified as an asymptomatic carrier of the pathogen associated with typhoid fever. She was presumed to have infected 22 people, three of whom died, over the course of her career as a cook. (Public Domain).

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SECTION OVERVIEW

10.1: Principles of Epidemiology

Epidemiology is the study of the patterns, causes, and effects of health and disease conditions in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results. Epidemiology has helped develop methodology used in clinical research, public health studies and, to a lesser extent, basic research in the biological sciences.

Topic hierarchy

10.1A: History of Epidemiology

10.1B: The Science of Epidemiology

10.1C: The Vocabulary Epidemiology

10.1D: Koch's Postulates

10.1E: Exceptions to Koch's Postulates

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10.1A: History of Epidemiology

Learning Objectives

- Describe the key events in the development of the field of epidemiology

Epidemiology is the study of the patterns, causes, and effects of health and disease conditions in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results. Epidemiology has helped develop methodology used in clinical research, public health studies and, to a lesser extent, basic research in the biological sciences.

The Greek physician Hippocrates is known as the father of medicine, and was the first epidemiologist. Hippocrates sought a logic to sickness. He is the first person known to have examined the relationships between the occurrence of disease and environmental influences. Hippocrates believed sickness of the human body to be caused by an imbalance of the four Humors (air, fire, water and earth “atoms”). The cure to the sickness was to remove or add the humor in question to balance the body. This belief led to the application of bloodletting and dieting in medicine.

The distinction between “epidemic” and “endemic” was first drawn by Hippocrates, to distinguish between diseases that are “visited upon” a population (epidemic) from those that “reside within” a population (endemic). The term “epidemiology” appears to have first been used to describe the study of epidemics in 1802 by the Spanish physician Joaquín de Villalba in Epidemiología Española. Epidemiologists also study the interaction of diseases in a population, a condition known as a syndemic.

One of the earliest theories on the origin of disease was that it was primarily the fault of human luxury. This was expressed by philosophers such as Plato and Rousseau, and social critics like Jonathan Swift. In the middle of the 16th century, a doctor from Verona named Girolamo Fracastoro was the first to propose a theory that these very small, unseeable, particles that cause disease were alive. They were considered to be able to spread by air, multiply by themselves and to be destroyable by fire. In 1543 he wrote a book De contagione et contagiosis morbis, in which he was the first to promote personal and environmental hygiene to prevent disease. The development of a sufficiently powerful microscope by Anton van Leeuwenhoek in 1675 provided visual evidence of living particles consistent with a germ theory of disease.

Dr. John Snow is famous for his investigations into the causes of the 19th century cholera epidemics, and is also known as the father of (modern) epidemiology. He began by noticing the significantly higher death rates in two areas supplied by Southwark Company. His identification of the Broad Street pump as the cause of the Soho epidemic is considered the classic example of epidemiology. He used chlorine in an attempt to clean the water and had the handle removed, thus ending the outbreak. This has been perceived as a major event in the history of public health and regarded as the founding event of the science of epidemiology, having helped shape public health policies around the world. However, Snow’s research and preventive measures to avoid further outbreaks were not fully accepted or put into practice until after his death.



Figure: ***Snow cholera map****: A variant of the original map drawn by Dr. John Snow (1813-1858), a British physician who is one of the founders of medical epidemiology, showing cases of cholera in the London epidemics of 1854, clustered around the locations of water pumps.*

In the early 20th century, mathematical methods were introduced into epidemiology by Ronald Ross, Anderson Gray McKendrick and others. Another breakthrough was the 1954 publication of the results of a British Doctors Study, led by Richard Doll and Austin Bradford Hill, which lent very strong statistical support to the suspicion that tobacco smoking was linked to lung cancer.

Key Points

- The Greek physician Hippocrates is known as the father of medicine, and was the first epidemiologist.
- The distinction between ” epidemic ” and “endemic” was first drawn by Hippocrates, to distinguish between diseases that are “visited upon” a population (epidemic) from those that “reside within” a population (endemic).
- In the early 20th century, mathematical methods were introduced into epidemiology adding statistical support to the field (i.e. the suspicion that tobacco smoking was linked to lung cancer was backed by statistics).

Key Terms

- **endemic**: (Especially of diseases.) Prevalent in a particular area or region.
- **epidemic**: A widespread disease that affects many individuals in a population.
- **epidemiology**: The branch of a science dealing with the spread and control of diseases, computer viruses, concepts, etc., throughout populations or systems.

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10.1B: The Science of Epidemiology

Epidemiological studies include disease etiology, disease surveillance and screening, biomonitoring, and clinical trials.

Learning Objectives

- Discuss the various factors that characterize epidemiology

Key Points

- Epidemiologists rely on other scientific disciplines like biology to better understand disease processes, statistics to make efficient use of the data and draw appropriate conclusions, social sciences to better understand proximate and distal causes, and engineering for exposure assessment.
- Epidemiologists employ a range of study designs from the observational to experimental. Its study designs are generally categorized as descriptive, analytical, and experimental.
- The identification of causal relationships between disease exposures and outcomes is an important aspect of epidemiology.

Key Terms

- **epidemiologist**: A scientist (often a medical doctor) who specializes in epidemiology.
- **causal**: A cause of something; causing.

Major areas of epidemiological study include disease etiology, outbreak investigation, disease surveillance and screening, biomonitoring, and comparisons of treatment effects such as in clinical trials. Epidemiologists rely on other scientific disciplines like biology to better understand disease processes, statistics to make efficient use of the data and draw appropriate conclusions, social sciences to better understand proximate and distal causes, and engineering for exposure assessment.

Epidemiological studies are aimed, where possible, at revealing unbiased relationships between exposures such as alcohol or smoking, biological agents, stress, or chemicals to mortality or morbidity. Epidemiologists employ a range of study designs from the observational to experimental. Its study designs are generally categorized as descriptive, analytical (aiming to further examine known associations or hypothesized relationships), and experimental (a term often equated with clinical or community trials of treatments and other interventions).

In observational studies, nature is allowed to “take its course”, as epidemiologists observe from the sidelines. Observational studies have two components: descriptive or analytical. Descriptive observations pertain to the “who, what, where and when of health-related state occurrence”. On the other hand, analytical observations deal more with the “how” of a health-related event.

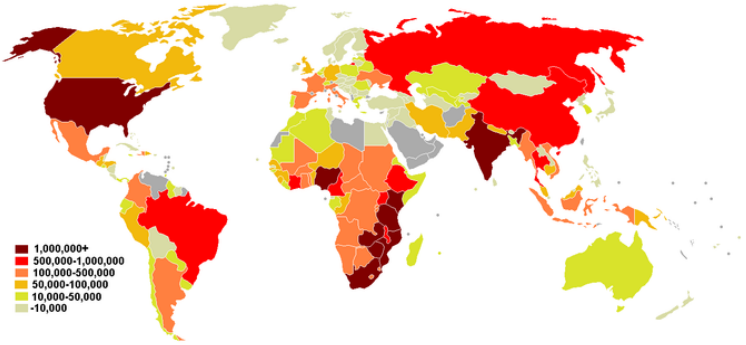

Figure: **World map of people living with HIV/AIDS**: This map captures the estimated number of people in the world living with HIV/AIDS in 2008.

Controversially, in experimental studies, the epidemiologist is the one in control of all of the factors relating to the particular case study. Experimental epidemiology contains three case types: randomized control trials (often used for new medicine or drug testing), field trials (conducted on those at a high risk of conducting a disease), and community trials (research on social originating diseases).

The identification of causal relationships between these exposures and outcomes is an important aspect of epidemiology. It is nearly impossible to say with perfect accuracy how even the most simple physical systems behave beyond the immediate future.

The complex field of epidemiology, which draws on biology, sociology, mathematics, statistics, anthropology, psychology, and policy only makes analysis even more challenging.

A common theme in much of the epidemiological literature is that “correlation does not imply causation. ” For epidemiologists, the key is in the term inference. Epidemiologists use gathered data and a broad range of biomedical and psychosocial theories in an iterative way to generate or expand theory, to test hypotheses, and to make educated, informed assertions about which relationships are causal, and about exactly how they are causal.

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10.1C: The Vocabulary Epidemiology

Learning Objectives

- Compare and contrast the following concepts: epidemic, endemic, pandemic; incidence vs prevalence; morbidity vs mortality; incubation, latency, acute, decline and convalescent periods

Epidemiology, literally meaning "the study of what is upon the people", is derived from Greek: *epi*, meaning "upon, among", *demos*, meaning "people, district", and *logos*, meaning "study, word, discourse", suggesting that it applies only to human populations. However, the term is widely used in studies of zoological populations (veterinary epidemiology) and of plant populations (botanical or plant disease epidemiology).

Outbreak is a term used in epidemiology to describe an occurrence of disease greater than would otherwise be expected at a particular time and place. It may affect a small and localized group or impact upon thousands of people across an entire continent. An *asymptomatic* carrier (healthy carrier or just carrier) is a person or other organism that has contracted an infectious disease, but who displays no symptoms. Although unaffected by the disease themselves, carriers can transmit it to others. A number of animal species act as vectors of human diseases.



Figure: **Mary Mallon**: Mary Mallon (1870-1938) was nicknamed "Typhoid Mary," an asymptomatic carrier of typhoid fever. She worked as a cook for several families in New York City at the beginning of the 20th century and infected many of them with typhoid. Note that in this 1909 newspaper illustration, she casts skulls into the skillet. However, this drawing inaccurately depicts the spread of typhoid, which was not by breathing, but by direct contamination from fecal particles.

EPIDEMIC, ENDEMIC OR PANDEMIC?

The distinction between "epidemic" and "endemic" was first drawn by Hippocrates, to distinguish between diseases that are "visited upon" a population (*epidemic*) from those that "reside within" a population (*endemic*). A *pandemic* is an epidemic of infectious disease that has spread through human populations across a large region; for instance multiple continents, or even worldwide. The term epidemiology is now widely applied to cover the description and causation of not only epidemic disease, but of disease in general, and even many non-disease health-related conditions, such as high blood pressure and obesity.

INCIDENCE VS. PREVALENCE

Incidence is a measure of the risk of developing some new condition within a specified period of time. Although sometimes loosely expressed simply as the number of new cases during a time period, it is better expressed as the incidence rate which is the number of new cases per population in a given time period. Incidence should not be confused with *prevalence*, which is a measure of the total number of cases of disease in a population rather than the rate of occurrence of new cases. Thus, incidence conveys

information about the risk of contracting the disease, whereas prevalence indicates how widespread the disease is. Prevalence is the proportion of the total number of cases to the total population and is more a measure of the burden of the disease on society.

MORBIDITY VS. MORTALITY

Morbidity is a diseased state, disability, or poor health due to any cause. The term may be used to refer to the existence of any form of disease, or to the degree that a health condition affects the patient. In epidemiology, the term morbidity rate can refer to either the incidence rate, or the prevalence of a disease, or medical condition. This measure of sickness is contrasted with the *mortality* rate of a condition, which is the proportion of people dying during a given time interval.

PHASES OF DISEASES

Epidemiologists are interested in determining the progression of a disease. In an infectious disease, the *incubation period* is the time between infection and the appearance of symptoms (acute period). The*latency period* is the time between infection and the ability of the disease to spread to another person, which may precede, follow, or be simultaneous with the appearance of symptoms. In most illnesses, the *acute period* is followed by the *decline period* (symptoms get better) and *convalescent* (or recovery) period.

Some viruses also exhibit a dormant phase, called *viral latency*, in which the virus hides in the body in an inactive state. For example, varicella zoster virus causes chickenpox in the acute phase; after recovery from chickenpox, the virus may remain dormant in nerve cells for many years, and later cause herpes zoster (shingles).

Key Points

- Outbreak is a term used in epidemiology to describe an occurrence of disease greater than would otherwise be expected at a particular time and place.
- An asymptomatic carrier is a person or other organism that has contracted an infectious disease, but who displays no symptoms.
- Diseases that are “visited upon” a population are epidemic, whereas those that “reside within” a population are endemic. A pandemic is an epidemic of infectious disease that has spread through human populations across a large region.
- Incidence is a measure of the risk of developing some new condition within a specified period of time. Prevalence is a measure of the total number of cases of disease in a population.
- Morbidity is a diseased state, disability, or poor health due to any cause. The mortality rate of a condition is the proportion of people dying from it during a given time interval.
- The progression of an infection usually follows these phases: infection, incubation period, acute period, decline period, and convalescent period.

Key Terms

- epidemiology: The branch of a science dealing with the spread and control of diseases, computer viruses, concepts, etc., throughout populations or systems.

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10.1D: Koch's Postulates

Learning Objectives

- List Koch's postulates

Koch's postulates are four criteria designed to establish a causal relationship between a causative microbe and a disease. The postulates were formulated by Robert Koch and Friedrich Loeffler in 1884 and refined and published by Koch in 1890. Koch applied the postulates to establish the etiology of anthrax and tuberculosis, but they have been generalized to other diseases.

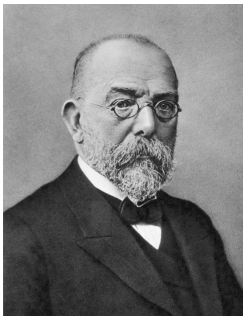

Figure: ***Robert Koch****: Robert Koch circa 1900. Koch's postulates are four criteria designed in the 1880's to establish a causal relationship between a causative microbe and a disease.*

Koch's postulates were developed in the 19th century as general guidelines to identify pathogens that could be isolated with the techniques of the day. Even in Koch's time, it was recognized that some infectious agents were clearly responsible for disease even though they did not fulfill all of the postulates. Attempts to rigidly apply Koch's postulates to the diagnosis of viral diseases in the late 19th century, at a time when viruses could not be seen or isolated in culture, may have impeded the early development of the field of virology. Currently, a number of infectious agents are accepted as the cause of disease despite their not fulfilling all of Koch's postulates. Therefore, while Koch's postulates retain historical importance and continue to inform the approach to microbiologic diagnosis, fulfillment of all four postulates is not required to demonstrate causality.

Koch's postulates

Koch's postulates are the following:

1. The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

Koch's postulates have also influenced scientists who examine microbial pathogenesis from a molecular point of view. In the 1980s, a molecular version of Koch's postulates was developed to guide the identification of microbial genes encoding virulence factors.

Key Points

- The postulates were formulated by Robert Koch and Friedrich Loeffler in 1884 and refined and published by Koch in 1890.
- Postulate 1: The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.
- Postulate 2: The microorganism must be isolated from a diseased organism and grown in pure culture.
- Postulate 3: The cultured microorganism should cause disease when introduced into a healthy organism.
- Postulate 4: The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

Key Terms

- **Koch's postulates**: four criteria designed to establish a causal relationship between a causative microbe and a disease
- **postulate**: A fundamental element; a basic principle.

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10.1E: Exceptions to Koch's Postulates

Learning Objectives

- Recognize the exception to Koch's postulates

Koch's postulates were developed in the 19th century as general guidelines to identify pathogens that could be isolated with the techniques of the day. Even in Koch's time, it was recognized that some infectious agents were clearly responsible for disease, even though they did not fulfill all of the postulates. Currently, a number of infectious agents are accepted as the cause of diseases despite their not fulfilling all of Koch's postulates. Therefore, while Koch's postulates retain historical importance and continue to inform the approach to microbiologic diagnosis, fulfillment of all four postulates is not required to demonstrate causality.

Koch abandoned the requirement of the first postulate altogether when he discovered asymptomatic carriers of cholera and, later, of typhoid fever. Asymptomatic or subclinical infection carriers are now known to be a common feature of many infectious diseases, especially viruses such as polio, herpes simplex, HIV, and hepatitis C. Specifically, all doctors and virologists agree that the poliovirus causes paralysis in just a few infected subjects, and the success of the polio vaccine in preventing disease supports the conviction that the poliovirus is the causative agent.

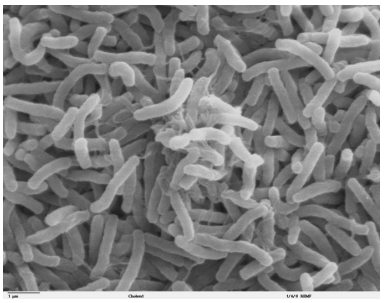

Figure: ***Cholera bacteria****: Scanning electron microscope image of Vibrio cholerae bacteria, which infect the digestive system.*

The second postulate may also be suspended for certain microorganisms or entities that cannot (at the present time) be grown in pure culture, such as prions responsible for Creutzfeldt–Jakob disease.

The third postulate specifies "should", not "must", because as Koch himself proved in regard to both tuberculosis and cholera, that not all organisms exposed to an infectious agent will acquire the infection. Noninfection may be due to such factors as general health and proper immune functioning; acquired immunity from previous exposure or vaccination; or genetic immunity, as with the resistance to malaria conferred by possessing at least one sickle cell allele.

In summary, a body of evidence that satisfies Koch's postulates is sufficient but not necessary to establish causation.

Key Points

- Koch abandoned the requirement of the first postulate altogether when he discovered asymptomatic carriers of cholera.
- The second postulate may also be suspended for certain microorganisms or entities that cannot (at the present time) be grown in pure culture, such as prions responsible for Creutzfeldt–Jakob disease.
- The third postulate specifies "should", not "must", because as Koch himself proved in regard to both tuberculosis and cholera, not all organisms exposed to an infectious agent will acquire the infection.

Key Terms

- **asymptomatic**: not exhibiting any symptoms of disease.

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SECTION OVERVIEW

10.2: Pathogen Identification

10.2A: Occurrence of a Disease

10.2B: Disease Severity and Duration

10.2C: Extent of Host Involvement

10.2D: Identification of Microbes Based on Molecular Genetics

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10.2A: Occurrence of a Disease

Learning Objectives

- Recognize the steps taken by epidemiologists when investigating disease outbreaks

Outbreak is a term used in epidemiology to describe an occurrence of disease greater than would otherwise be expected at a particular time and place. It may affect a small and localized group or impact thousands of people across an entire continent. Two linked cases of a rare infectious disease may be sufficient to constitute an outbreak. Outbreaks may also refer to endemics that affect a particular place or group, epidemics that affect a region in a country or a group of countries, and pandemics that describe global disease outbreaks.



Figure: **1918 Flu Victims**: With masks over their faces, members of the American Red Cross remove a victim of the Spanish Flu from a house at Etzel and Page Avenues, St. Louis, Missouri.

The epidemiology profession has developed a number of widely accepted steps when investigating disease outbreaks. As described by the Centers for Disease Control and Prevention, these include the following:

1. Verify the diagnosis related to the outbreak.
2. Identify the existence of the outbreak (if the group of ill persons is normal for the time of year, geographic area, etc.).
3. Create a case definition to define who/what is included as a case.
4. Map the spread of the outbreak.
5. Develop a hypothesis (if there appears to be a cause for the outbreak).
6. Study hypothesis (collect data and perform analysis).
7. Refine hypothesis and carry out further study.
8. Develop and implement control and prevention systems.
9. Release findings to greater communities.

There are several outbreak patterns that can be useful in identifying the transmission method or source and predicting the future rate of infection.

1. Common source – All victims acquire the infection from the same source (e.g. a contaminated water supply).
2. Continuous source – Common source outbreak where the exposure occurs over multiple incubation periods.
3. Point source – Common source outbreak where the exposure occurs in less than one incubation period.
4. Propagated – Transmission occurs from person to person.

Each has a distinctive epidemic curve, or histogram of case infections and deaths.

Outbreaks can also be:

1. Behavioral risk related (e.g. sexually transmitted diseases, increased risk due to malnutrition)
2. Zoonotic – The infectious agent is endemic to an animal population.

Key Points

- Outbreaks may also refer to endemics that affect a particular place or group, epidemics that affect a region in a country or a group of countries, or pandemics that describe global disease outbreaks.
- The epidemiology profession has developed a number of widely accepted steps to investigate a disease occurrence.

- Outbreak patterns, which can be useful in identifying the transmission method or source, and predicting the future rate of infection include common source, continuous source, point source, and propagated source.
- Outbreaks can be behavioral risk related (e.g., sexually transmitted diseases, increased risk due to malnutrition) or zoonotic (e.g. the infectious agent is endemic to an animal population).

Key Terms

- **outbreak**: A term used in epidemiology to describe an occurrence of disease greater than would otherwise be expected at a particular time and place.
- **epidemic**: A widespread disease that affects many individuals in a population.
- **pandemic**: A disease that hits a wide geographical area and affects a large proportion of the population.

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10.2B: Disease Severity and Duration

The severity and duration of diseases vary greatly and are important for epidemiological studies.

Learning Objectives

- Discuss the severity and various types of disease duration, including: acute, chronic, flare-up, refractory, progressive, remission and a cure

Key Points

- Severity of illness is defined as the extent of organ system derangement or physiologic decompensation of a patient, and in general an illness is classified into minor, moderate, major, and extreme.
- In an infectious disease, the incubation period is the time between infection and the appearance of symptoms, the latency period is the time between infection and the ability to spread to another person, and the viral latency is the time the virus hides in the body in an inactive state.
- Disease duration can encompass one or more of the following: an acute disease, a chronic disease, a flare-up, a refractory disease is a disease, a progressive disease, or a cure.
- The scope of a disease, whether it is localized, disseminated, or systemic also affects its severity and duration.
- The International Classification of Diseases (ICD) is known as a health care classification system that provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease.

Key Terms

- **severity**: the degree of something undesirable; badness or seriousness.
- **duration**: an amount of time or a particular time interval

Severity of illness is defined as the extent of organ system derangement or physiologic decompensation of a patient. It gives a medical classification into minor, moderate, major, and extreme that is meant to provide a basis for evaluating hospital resource use or to establish patient care guidelines.

In an infectious disease, the incubation period is the time between infection and the appearance of symptoms. The latency period is the time between infection and the ability of the disease to spread to another person, which may precede, follow, or be simultaneous with the appearance of symptoms. Some viruses also exhibit a dormant phase, called viral latency, in which the virus hides in the body in an inactive state.

Disease duration can be one of the following:

1. An acute disease is a short-lived disease, like the common cold.
2. A chronic disease is one that lasts for a long time, usually at least six months. During that time, it may be constantly present, or it may go into remission and periodically relapse. A chronic disease may be stable (does not get any worse) or it may be progressive (gets worse over time). Some chronic diseases can be permanently cured. Most chronic diseases can be beneficially treated, even if they cannot be permanently cured.
3. A flare-up can refer to either the recurrence of symptoms or an onset of more severe symptoms.
4. A refractory disease is a disease that resists treatment, especially an individual case that resists treatment more than is normal for the specific disease in question.
5. A progressive disease is a disease whose typical natural course is the worsening of the disease until death, serious debility, or organ failure occurs. Slowly progressive diseases are also chronic diseases; many are also degenerative diseases. The opposite of progressive disease is stable disease or static disease: a medical condition that exists, but does not get better or worse.
6. A cure is the end of a medical condition or a treatment that is very likely to end it, while remission refers to the disappearance, possibly temporarily, of symptoms. Complete remission is the best possible outcome for incurable diseases.

The scope of a disease also affects its severity and duration:

1. A localized disease is one that affects only one part of the body, such as athlete's foot or an eye infection.
2. A disseminated disease has spread to other parts; with cancer, this is usually called metastatic disease.
3. A systemic disease is a disease that affects the entire body, such as influenza or high blood pressure.

The International Classification of Diseases (most commonly known by the abbreviation ICD) is according to its publisher, the United Nations-sponsored World Health Organization, and is considered “the standard diagnostic tool for epidemiology, health management and clinical purposes. ” It is known as a health care classification system that provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. Under this system, every health condition can be assigned to a unique category and given a code, up to six characters long. Such categories can include a set of similar diseases.The International Classification of Diseases is published by the World Health Organization (WHO) and is used worldwide for morbidity and mortality statistics, reimbursement systems, and automated decision support in health care. This system is designed to promote international comparability in the collection, processing, classification, and presentation of these statistics. The ICD is a core classification of the WHO Family of International Classifications (WHO-FIC).

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10.2C: Extent of Host Involvement

Host-pathogen interactions are the interactions taking place between a pathogen (e.g. virus, bacteria) and their host (e.g. humans, plants).

Learning Objectives

- Differentiate between primary and opportunistic pathogens in regards to host involvement

Key Points

- All pathogens damage their host to some extent, usually resulting in an infectious disease from the interplay between the pathogens and the defenses of the hosts they infect.
- Clinicians classify infectious microorganisms or microbes according to the status of host defenses – either as primary pathogens or as opportunistic pathogens.
- Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host, and their intrinsic virulence is, in part, a necessary consequence of their need to reproduce and spread.
- Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens.

Key Terms

- **host**: A cell or organism which harbors another organism or biological entity, usually a parasite.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.

Host-pathogen interactions are the interactions that take place between a pathogen (e.g. virus, bacteria) and their host (e.g. humans, plants). By definition, all pathogens damage their host to some extent. Infectious diseases result from the interplay between the pathogens and the defenses of the hosts they infect. The appearance and severity of disease resulting from the presence of any pathogen depends upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen.

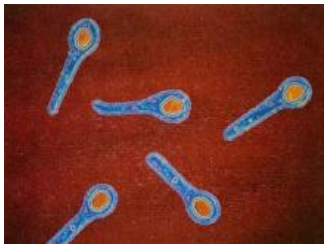

Figure: **Clostridium tetani**: Clostridium tetani are pathogenic bacteria.

Clinicians therefore classify infectious microorganisms or microbes according to the status of host defenses – either as primary pathogens or as opportunistic pathogens.

Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host, and their intrinsic virulence is, in part, a necessary consequence of their need to reproduce and spread. Many of the most common primary pathogens of humans only infect humans; however many serious diseases are caused by organisms acquired from the environment or which infect non-human hosts.

Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens. Opportunistic diseases may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal or the upper respiratory tract, and they may also result from (otherwise innocuous) microbes acquired from other hosts or from the environment as a result of traumatic introduction. An opportunistic disease requires impairment of host defenses, which may occur as a result of several factors such as genetic defects, exposure to antimicrobial drugs or immunosuppressive chemicals, exposure to ionizing radiation, or as a result of an infectious disease with immunosuppressive activity. Primary pathogens may also cause more severe disease in a host with depressed resistance than would normally occur in an immunosufficient host.

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10.2D: Identification of Microbes Based on Molecular Genetics

Modern nucleic acid-based microbial detection methods make it possible to identify microbes that are associated with a disease.

Learning Objectives

- Describe the components of Molecular Koch's postulates

Key Points

- Nucleic acid -based detection methods are very sensitive.
- Molecular Koch's postulates are a set of experimental criteria that must be satisfied to show that a gene found in a pathogenic microorganism encodes a product that contributes to the disease caused by the pathogen.
- After virulent factors have been identified, it is possible to develop a vaccine against the factors.
- For many pathogenic microorganisms, it is not currently possible to apply molecular genetic techniques to a gene in question.

Key Terms

- **genetic**: Relating to genetics or genes.
- **nucleic acid**: Any acidic, chainlike biological macromolecule consisting of repeating units of phosphoric acid, sugar, and purine and pyrimidine bases; they are involved in the preservation, replication, and expression of hereditary information in every living cell.
- **virulent**: Highly infectious, malignant, or deadly.
- **genetics**: the branch of biology that deals with the transmission and variation of inherited characteristics, in particular chromosomes and DNA

Modern nucleic acid-based microbial detection methods make it possible to identify microbes that are associated with a disease. Nucleic acid-based detection methods are very sensitive, and they can often detect the very low levels of viruses that are found in healthy people without disease.

The use of these new methods has led to revised versions of Koch's postulates. Molecular Koch's postulates are a set of experimental criteria that must be satisfied to show that a gene found in a pathogenic microorganism encodes a product that contributes to the disease caused by the pathogen. Genes that satisfy molecular Koch's postulates are often referred to as virulence factors (i.e., what makes the pathogen virulent). The following set of Koch's postulates for the 21st century have been suggested:

1. A nucleic acid sequence belonging to a putative pathogen should be present in most cases of an infectious disease. Microbial nucleic acids should be found, preferentially in those organs or gross anatomic sites known to be diseased and not in those organs that lack pathology.
2. Fewer, or no, copies of the pathogen-associated nucleic acid sequences should occur in hosts or tissues without disease.
3. With resolution of the disease, the copy number of pathogen-associated nucleic acid sequences should decrease or become undetectable. With clinical relapse, the opposite should occur.
4. When sequence detection predates disease, or the sequence copy number correlates with severity of disease or pathology, the sequence-disease association is more likely to be a causal relationship.
5. The nature of the microorganism inferred from the available sequence should be consistent with the known biological characteristics of that group of organisms.
6. Tissue-sequence correlates should be sought at the cellular level. Efforts should be made to demonstrate specific in situ hybridization of microbial sequence to areas of tissue pathology and to visible microorganisms or to areas where microorganisms are presumed to be located.
7. These sequence-based forms of evidence for microbial causation should be reproducible.

Once virulent factors have been identified, it is possible to develop a vaccine against the factors. illustrates how the avian flu vaccine was developed using reverse genetic techniques.

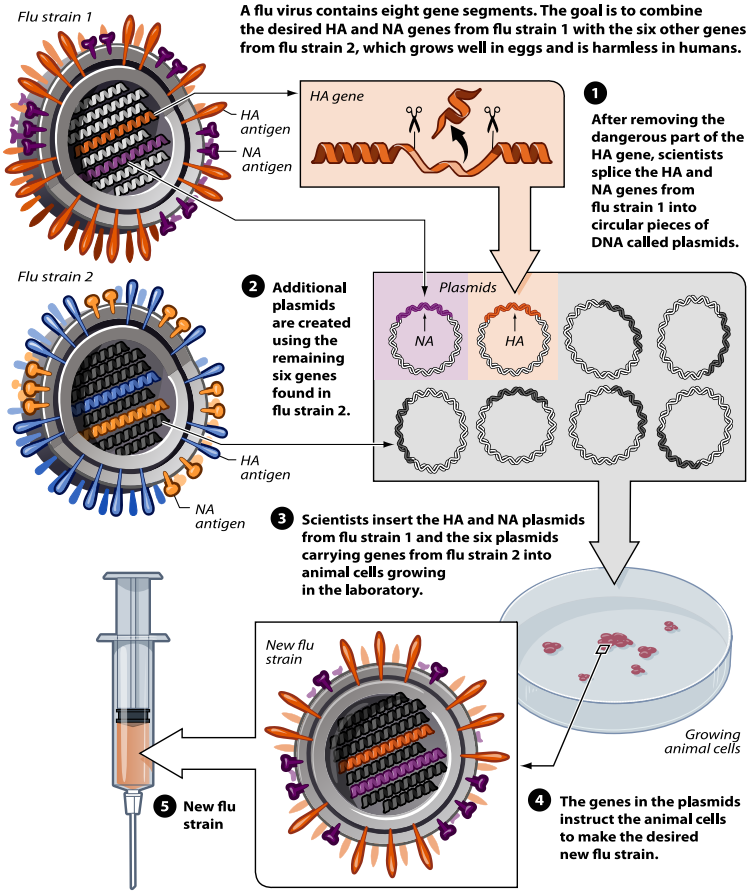

Figure: **Reserve genetics**: Avian flu vaccine development by reverse genetics technique.

For many pathogenic microorganisms, it is not currently possible to apply molecular genetic techniques to a gene in question. Testing a candidate virulence gene requires a relevant animal model of the disease being examined and the ability to genetically manipulate the microorganism that causes the disease. Suitable animal models are lacking for many important human diseases. Additionally, many pathogens cannot be manipulated genetically.

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SECTION OVERVIEW

10.3: Disease Patterns

10.3A: Predisposing Factors

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10.3C: Disease Reservoirs and Epidemics

10.3D: Infectious Disease Transmission

10.3E: Ecology, Epidemiology, and Evolution of Pathogens

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10.3G: Finding Patient Zero and Tracking Diseases

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10.3A: Predisposing Factors

The spread and severity of infectious disease is influenced by many predisposing factors.

Learning Objectives

- Recognize factors that are classified as predisposing to infectious disease

Key Points

- Some predisposing factors of contracting infectious diseases can be anatomical, genetic, general and disease specific.
- Climate and weather, and other environmental factors that are affected by them, can also predispose people to infectious agents.
- Other factors such as overall health, age and diet are important considerations in the prevention of spreading infectious diseases.

Key Terms

- **cystic fibrosis**: Cystic fibrosis (also known as CF or mucoviscidosis) is an autosomal recessive genetic disorder that affects most critically the lungs, and also the pancreas, liver and intestine. It is characterized by abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions.
- **Chronic granulomatous disease**: Also known as CGD, is a diverse group of genetic diseases in which certain cells of the immune system have difficulty forming the reactive oxygen compounds (most importantly, the superoxide radical) used to kill certain ingested pathogens. This leads to the formation of granulomata (a special type of inflammation) in many organs.

The spread and severity of infectious disease is influenced by many predisposing factors. Some of these are more general and apply to many infectious agents, while others are disease specific. Others can be anatomical. For example, women suffer more frequently from urinary tract infections which can be attributed to their shorter urethra.

Genetics is another contributing factor. Cystic fibrosis is a genetic disease that causes alteration of the mucus in the lungs. This predisposes patients to chronic infections with bacteria which form biofilms in the lungs. The most common infectious agent is *Pseudomonas aeruginosa*. Another example is chronic granulomatous disease which directly affects the ability of the host immune system to fight invaders.

Climate and weather, and other environmental factors that are affected by them, can also predispose people to infectious agents. A long-standing puzzle has been why flu outbreaks occur seasonally. One possible explanation is that, because people are indoors more often during the winter, they are in close contact more often, and this promotes transmission from person to person. Another factor is that cold temperatures lead to drier air, which may dehydrate mucus, preventing the body from effectively expelling virus particles. The virus also survives longer on surfaces at colder temperatures and aerosol transmission of the virus is highest in cold environments (less than 5°C) with low relative humidity. Indeed, the lower air humidity in winter seems to be the main cause of seasonal influenza transmission in temperate regions. Some scientists speculate that the seasonal fluctuations of vitamin D levels can be a factor in the spread of influenza too.

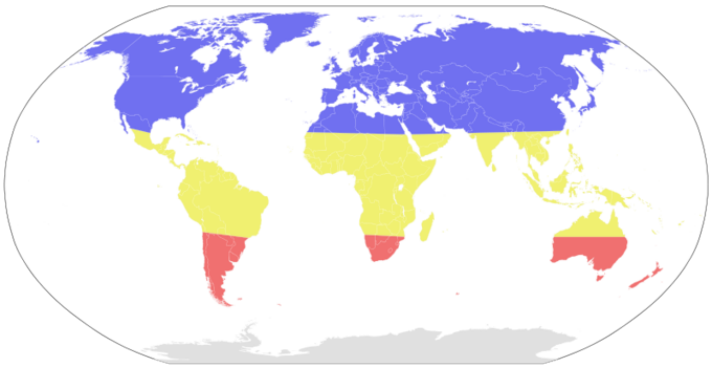

Figure: **Global map of Seasonal Influenza**: Seasonal risk areas: November–April (blue), April–November (red), and year-round (yellow)

Overall health is a very important factor in preventing disease. Some portions of the immune system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions. In general, deliberately-induced immunosuppression is performed to prevent the body from rejecting an organ

transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease. Of course, the immune system can be weak due to other reasons such as chemotherapy and HIV.

Age is another critical factor. Newborns and infants are more susceptible to infections as are the elderly.

Inadequate diet can raise the risks too. For example, globally, the severe malnutrition common in parts of the developing world causes a large increase in the risk of developing active tuberculosis and other opportunistic infections, due to its damaging effects on the immune system. Along with overcrowding, poor nutrition may contribute to the strong link observed between tuberculosis and poverty.

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10.3B: Disease Development

After an pathogen invades a host, it undergoes a series of phases that eventually lead to multiplication of the pathogen.

Learning Objectives

- Outline the stages of disease: incubation, prodromal, acute and convalescence periods

Key Points

- The first phase is characterized by complete lack or very few symptoms.
- As the pathogen starts to reproduce actively, the symptoms intensify. Bacterial and viral infections can both cause the same kinds of symptoms but there are some differences too.
- The last phases are characterized by decline in symptoms severity until their disappearance. However, even if the patients recover and return to normal, they may continue to be a source of infection.

Key Terms

- **subclinical**: Of a disease or injury, without signs and symptoms that are detectable by physical examination or laboratory test; not clinically manifest.
- **clinical latency**: The period for which an infection is subclinical.
- **viral latency**: A form of viral dormancy in which the virus does not replicate at all.

Stages of Disease

After an infectious agent invades a host (patient), it undergoes a series of phases (stages) that will eventually lead to its multiplication and release from the host.

STAGE 1: INCUBATION PERIOD

This refers to the time elapsed between exposure to a pathogenic organism, and from when symptoms and signs are first apparent. It may be as short as minutes to as long as thirty years in the case of variant Creutzfeldt–Jakob disease. While the term latency period is used as synonymous, a distinction is sometimes made between incubation period, the period between infection and clinical onset of the disease, and latent period, the time from infection to infectiousness. Whichever is shorter depends on the disease.

A person may be a carrier of a disease, such as *Streptococcus* in the throat, without exhibiting any symptoms. Depending on the disease, the person may or may not be contagious during the incubation period. During clinical latency, an infection is subclinical. With respect to viral infections, in clinical latency the virus is actively replicating. This is in contrast to viral latency, a form of dormancy in which the virus does not replicate.

STAGE 2: PRODROMAL PERIOD

In this phase, the numbers of the infectious agents start increasing and the immune system starts reacting to them. It is characterized by early symptoms that might indicate the start of a disease before specific symptoms occur. Prodromes may be non-specific symptoms or, in a few instances, may clearly indicate a particular disease. For example fever, malaise, headache and lack of appetite frequently occur in the prodrome of many infective disorders. It also refers to the initial in vivo round of viral replication.

STAGE 3: ACUTE PERIOD

This stage is characterized by active replication or multiplication of the pathogen and its numbers peak exponentially, quite often in a very short period of time. Symptoms are very pronounced, both specific to the organ affected as well as in general due to the strong reaction of the immune system.

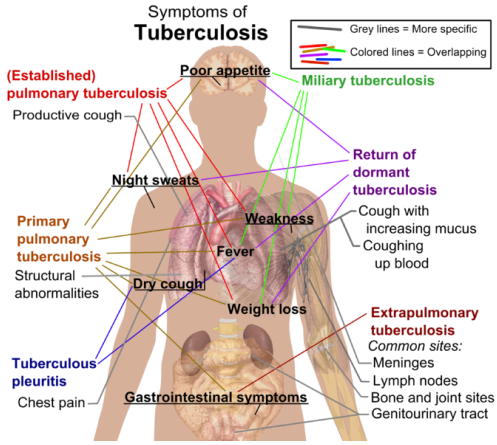

Figure: **Symptoms of tuberculosis**: Some of the symptoms are very specific for the disease while others are more general and can be caused by other pathogens.

Viral infections present with systemic symptoms. This means they involve many different parts of the body or more than one body system at the same time; i.e. a runny nose, sinus congestion, cough, body aches, etc. They can be local at times as in viral conjunctivitis or “pink eye” and herpes. Only a few viral infections are painful, like herpes. The pain of viral infections is often described as itchy or burning.

The classic symptoms of a bacterial infection are localized redness, heat, swelling and pain. One of the hallmarks of a bacterial infection is local pain, pain that is in a specific part of the body. For example, if a cut occurs and is infected with bacteria, pain occurs at the site of the infection. Bacterial throat pain is often characterized by more pain on one side of the throat. An ear infection is more likely to be diagnosed as bacterial if the pain occurs in only one ear.

After the pathogen reaches its peak in newly-produced cells or particles (for viruses), the numbers begin to fall sharply. Symptoms are still present but they are not as strong as in the acute illness phase.

STAGE 4: CONVALESCENCE PERIOD

The patient recovers gradually and returns to normal, but may continue to be a source of infection even if feeling better. In this sense, “recovery” can be considered a synonymous term.

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10.3C: Disease Reservoirs and Epidemics

Once discovered, natural reservoirs elucidate the complete life cycle of infectious diseases, providing effective prevention and control.

Learning Objectives

- Give examples of disease reservoirs and distinguish between common source and propagated outbreaks

Key Points

- Often the natural reservoirs for a human infectious disease are animals such as bats for SARS and rats for plague. Some diseases have no non-human reservoirs: poliomyelitis and smallpox are prominent examples. The natural reservoir of some diseases remains unknown.
- In epidemiology, an epidemic occurs when new cases of a certain disease, in a given human population, and during a given period, substantially exceed what is expected based on recent experience.
- An epidemic may be restricted to one location; however, if it spreads to other countries or continents and affects a substantial number of people, it may be termed a pandemic.
- There are two types of epidemic outbreak: (1) In a common source outbreak, the affected individuals had exposure to a common agent. (2) In a propagated outbreak, the disease spreads person-to-person.

Key Terms

- **pandemic**: A disease that hits a wide geographical area and affects a large proportion of the population.
- **common source outbreak**: a type of epidemic outbreak where the affected individuals had an exposure to a common agent.
- **propagated outbreak**: a type of epidemic outbreak where the disease spreads person-to-person. Affected individuals may become independent reservoirs leading to further exposures.

Disease Reservoirs

A natural reservoir refers to the long-term host of the pathogen of an infectious disease. It is often the case that hosts do not get the disease carried by the pathogen or it is carried as a subclinical infection and so remains asymptomatic and non-lethal.

Once discovered, natural reservoirs elucidate the complete life cycle of infectious diseases, providing effective prevention and control. Some examples of natural reservoirs of infectious diseases include:

- Bubonic plague: marmots, black rats, prairie dogs, chipmunks, and squirrels for bubonic plague
- Chagas disease: armadillos and opossums and several species of New World Leishmania
- Babeiosis and Rocky Mountain spotted fever: ticks
- Colorado tick fever: ground squirrels, porcupines, and chipmunks
- Rabies: raccoons, skunks, foxes, and bats
- Cholera: shellfish
- Severe acute respiratory syndrome (SARS): bats
- Ebola: fruit bats, subhuman primates, and antelope called duikers

Some diseases have no non-human reservoir: poliomyelitis and smallpox are prominent examples. The natural reservoirs of some diseases still remain unknown.

DISEASE EPIDEMICS

In epidemiology, an epidemic occurs when new cases of a certain disease, in a given human population, and during a given period, substantially exceed what is expected, based on recent experience. Epidemiologists often consider the term outbreak to be synonymous to epidemic, but the general public typically perceives outbreaks to be more local and less serious than epidemics.

Epidemics of infectious disease are generally caused by:

- a change in the ecology of the host population (e.g. increased stress or increase in the density of a vector species)
- a genetic change in the parasite population
- the introduction of a new parasite to a host population (by movement of parasites or hosts)

Generally, an epidemic occurs when host immunity to a parasite population is suddenly reduced below that found in the endemic equilibrium and the transmission threshold is exceeded.

An epidemic may be restricted to one location; however, if it spreads to other countries or continents and affects a substantial number of people, it may be termed a pandemic. The declaration of an epidemic usually requires a good understanding of a baseline rate of incidence. Epidemics for certain diseases, such as influenza, are defined as reaching some defined increase in incidence above this baseline.

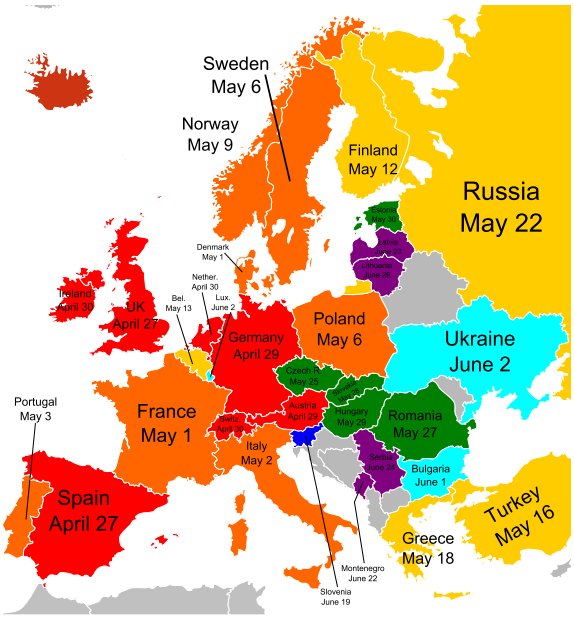

Figure: **Spread of H1N1 in Europe, 2009**: The World Health Organization declared the new flu strain H1N1 as a pandemic in June 2009.

A few cases of a very rare disease may be classified as an epidemic, while many cases of a common disease (such as the common cold) would not. An epidemic disease is not required to be contagious, and the term has been applied to West Nile fever.

EPIDEMIC OUTBREAKS

There are two types of epidemic outbreaks: (1) In a common source outbreak, the affected individuals had an exposure to a common agent. If the exposure is singular and all of the affected individuals develop the disease over a single exposure and incubation course, it can be termed a point-source outbreak. If the exposure was continuous or variable, it can be termed a continuous outbreak or intermittent outbreak, respectively.

(2) In a propagated outbreak, the disease spreads person-to-person. Affected individuals may become independent reservoirs leading to further exposures. Many epidemics will have characteristics of both common source and propagated outbreaks. For example, secondary person-to-person spread may occur after a common source exposure or environmental vectors may spread a zoonotic disease agent.

The conditions which govern the outbreak of epidemics include infected food supplies, such as drinking water contaminated by waste from people with cholera or typhoid fever or ‘fast food’ products contaminated with salmonella. The migrations of certain animals, such as rats, are in some cases responsible for the spread of plague, from which these animals die in great numbers.

Certain epidemics occur at certain seasons: for example, whooping-cough occurs in spring, whereas measles produces two epidemics – as a rule, one in winter and one in March. Influenza, the common cold, and other infections of the upper respiratory tract, such as sore throat, occur predominantly in the winter.

There is another variation, both as regards the number of persons affected and the number who die in successive epidemics: the severity of successive epidemics rises and falls over periods of five or ten years.

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10.3D: Infectious Disease Transmission

Defining the means of transmission of a pathogen is important in understanding its biology and in addressing the disease it causes.

Learning Objectives

- Give examples of various modes of transmission, including direct and indirect transmission

Key Points

- Infectious organisms may be transmitted either by direct or indirect contact.
- Transmission may occur through several different mechanisms. Transmission of infectious diseases may also involve a vector. Vectors may be mechanical or biological.
- Pathogens can also be transmitted horizontally or vertically.

Key Terms

- **fomite**: An inanimate object capable of carrying infectious agents (such as bacteria, viruses and parasites), and thus passively enabling their transmission between hosts.
- **aerosolized**: Dispersed as an aerosol; particulate.
- **vector**: A carrier of a disease-causing agent.

For infecting organisms to survive and repeat the infection cycle in other hosts, they (or their progeny) must leave an existing reservoir and cause infection elsewhere. Defining the means of transmission plays an important part in understanding the biology of an infectious agent and in addressing the disease it causes.

Infectious organisms may be transmitted either by direct or indirect contact. Direct contact occurs when an individual comes into contact with the reservoir. Indirect contact occurs when the organism is able to withstand the harsh environment outside the host for long periods of time and still remains infective when specific opportunity arises.

Transmission may occur through several different mechanisms. Respiratory diseases and meningitis are commonly acquired by contact with aerosolized droplets, spread by sneezing, coughing, talking, kissing, or even singing. Gastrointestinal diseases are often acquired by ingesting contaminated food and water. Washing hands is an effective measure to prevent contaminating food and water. A common method of transmission in under-developed countries is fecal-oral transmission. In such cases, sewage water is used to wash food or is consumed. Sexually transmitted diseases are acquired through contact with bodily fluids, generally as a result of sexual activity. Some infectious agents may be spread as a result of contact with a contaminated, inanimate object (known as a fomite), such as a coin passed from one person to another, while other diseases penetrate the skin directly.



Figure: **Washing Hands**: Washing hands with soap and clean water (for at least 20 seconds) is the most effective measure to prevent the spread of infectious diseases.

Transmission of infectious diseases may also involve a vector. Vectors may be mechanical or biological. A mechanical vector picks up an infectious agent on the outside of its body and transmits it in a passive manner. An example of a mechanical vector is a housefly, which lands on cow dung, contaminating its appendages with bacteria from the feces and then lands on food. The pathogen never enters the body of the fly.

In contrast, biological vectors harbor pathogens within their bodies and deliver pathogens to new hosts in an active manner, usually a bite. Biological vectors are often responsible for serious blood-borne diseases, such as malaria, viral encephalitis, Chagas disease, Lyme disease, and African sleeping sickness. Biological vectors are usually, though not exclusively, arthropods, such as mosquitoes, ticks, fleas, and lice. Vectors are often required in the life cycle of a pathogen. A common strategy used to control vector borne infectious diseases is to interrupt the life cycle of a pathogen by killing the vector.

All of the above modes are examples of horizontal transmission because the infecting organism is transmitted from person to person in the same generation. There are also a variety of infections transmitted vertically, that is from mother to child during the birthing process or fetal development. Common disorders transmitted this way include AIDs, hepatitis, herpes, and cytomegalovirus.

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10.3E: Ecology, Epidemiology, and Evolution of Pathogens

Pathogens have evolved to adapt to their environment and their host in order to survive.

Learning Objectives

- Discuss the contributing factors to pathogen evolution

Key Points

- Ecological competence is the ability of an organism, often a pathogen, to survive and compete in new habitats.
- Epidemiology is another important tool used to study disease in a population.
- In most cases, microorganisms live in harmony with their hosts via mutual or commensal interactions.
- Diseases can emerge when existing parasites become pathogenic or when new pathogenic parasites enter a new host.

Key Terms

- **zoonose**: Infectious diseases transmitted between different species of animals, usually from a vertebrate animal to a human
- **ecological competence**: The ability of an organism, often a pathogen, to survive and compete in new habitats.
- **virulence**: The degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host and it is determined by virulence factors.

Ecological competence is the ability of an organism, often a pathogen, to survive and compete in new habitats. If a pathogen does not have this, it will likely become extinct. In the case of plant pathogens, it is also their ability to survive between growing seasons. For example, peanut clump virus can survive in the spores of its fungal vector until a new growing season begins and it can proceed to infect its primary host again.

Epidemiology is another important tool used to study disease in a population. For infectious diseases, it helps to determine if a disease outbreak is sporadic (occasional occurrence), endemic (regular cases often occurring in a region), epidemic (an unusually high number of cases in a region), or pandemic (a global epidemic). The Black Death (plague) of the 14th century reduced the world population from an estimated 450 million to 350 – 375 million.

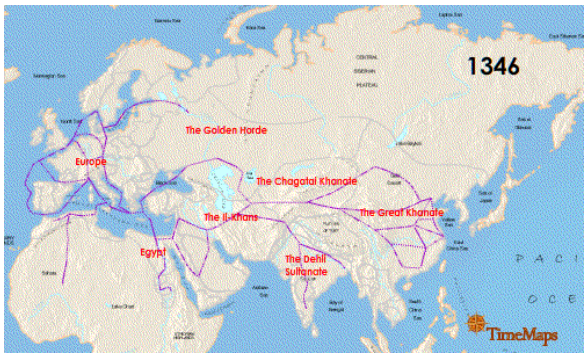

Figure: **The Black Death of the 14th century**: An animation of the plague that spread through the world during the pandemic in the 14th century.

In most cases, microorganisms live in harmony with their hosts via mutual or commensal interactions. Diseases can emerge when existing parasites become pathogenic or when new pathogenic parasites enter a new host. Coevolution between parasite and host can lead to hosts becoming resistant to the parasites or the parasites may evolve greater virulence, leading to immunopathological disease.

In addition, human activity is involved with many emerging infectious diseases, such as environmental change enabling a parasite to occupy new niches. When that happens, a pathogen that had been confined to a remote habitat has a wider distribution and possibly, a new host organism. Diseases transferred from nonhuman to human hosts are known as *zoonoses*.

Under disease invasion, when a parasite invades a new host species, it may become pathogenic in the new host. Several human activities have led to the emergence and spread of new diseases, such as encroachment on wildlife habitats, changes in agriculture, the destruction of rain forests, uncontrolled urbanization, modern transport.

According to evolutionary medicine, virulence increases with horizontal transmission (between non-relatives) and decreases with vertical transmission (from parent to child). Optimal virulence is a concept relating to the ecology of hosts and parasites. One definition of this is the host's parasite-induced loss of fitness. The parasite's fitness is determined by its success in transmitting its offspring to other hosts.

At one stage, the consensus was that over time, virulence moderated and parasitic relationships evolved toward symbiosis. This view has been challenged. A pathogen that is too restrained will lose out in competition to a more aggressive strain that diverts more host resources to its own reproduction. However, the host, being the parasite's resource and habitat in a way, suffers from this higher virulence. This might induce faster host death, and act against the parasite's fitness by reducing probability to encounter another host (killing the host too fast to allow for transmission).

Thus, there is a natural force providing pressure on the parasite to "self-limit" its virulence. The idea is then, that there exists an equilibrium point of virulence, where parasite's fitness is highest. Any movement on the virulence axis, towards higher or lower virulence, will result in lower fitness for the parasite, and this will be selected against.

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10.3F: Safety in the Microbiology Laboratory

Working with microorganisms, especially pathogens, requires special equipment and safety practices.

Learning Objectives

- Distinguish between the different biohazard levels 1, 2, 3 and 4

Key Points

- The CDC categorizes various diseases in levels of biohazard: Level 1 being minimum risk and Level 4 being extreme risk.
- BSL-1 lab is used to perform research mostly on noninfectious microbes using standard equipment and routine lab safety procedures.
- BSL-2 work is performed with bacteria and viruses that cause only mild disease to humans, or are difficult to contract via aerosol in a lab setting. Safety regulations are stricter.
- In a BSL-3 setting, the work is with bacteria and viruses that can cause severe to fatal disease in humans, but for which vaccines or other treatments exist. The laboratory has special engineering and design features.
- BSL-4 level is mandatory for research on viruses and bacteria that cause severe to fatal disease in humans, and for which no vaccines or treatments are available. The use of a positive-pressure personnel suit is mandatory as well as many additional safety measures of the labs.

Key Terms

- **biohazards**: Biological substances that pose a threat to the health of living organisms, especially humans.

Keeping Safe in the Laboratory

Working with microorganisms, especially pathogens, requires special equipment and safety practices. Biological hazards, also known as biohazards, refer to biological substances that pose a threat to the health of living organisms, especially humans. The biohazard symbol is used in the labeling of biological materials that carry a significant health risk, including viral samples and used hypodermic needles.



Figure: **Biohazard symbol**: The international symbol used to label biohazards.

The United States' Centers for Disease Control and Prevention (CDC) categorize various diseases in levels of biohazard: Level 1 being minimum risk and Level 4 being extreme risk. Laboratories and other facilities are categorized as BSL (Biosafety Level) 1-4 or as P1 through P4 for short (Pathogen or Protection Level).

BIOHAZARD LEVEL 1:

Bacteria and viruses including *Bacillus subtilis*, *Escherichia coli* , canine hepatitis, varicella (chicken pox), as well as some cell cultures and non- infectious bacteria. Work is generally conducted on open bench tops using standard microbiological practices. At this level, precautions against the biohazardous materials in question are minimal, most likely involving gloves and some sort of facial protection. Decontamination procedures are similar in most respects to modern precautions against everyday microorganisms (i.e., washing one's hands with anti-bacterial soap, washing all exposed surfaces of the lab with disinfectants, etc.). In a lab environment all materials used for cell and/or bacteria cultures are decontaminated via autoclave. Laboratory personnel have specific training in the procedures conducted in the laboratory and are supervised by a scientist with general training in microbiology or a related science.

BIOHAZARD LEVEL 2:

Bacteria and viruses that cause only mild disease to humans, or are difficult to contract via aerosol in a lab setting, such as hepatitis A, B, and C, influenza A, Lyme disease, salmonella, mumps, measles, scrapie, dengue fever, and HIV. BSL-2 differs from BSL-1 in that:

- laboratory personnel have specific training in handling pathogenic agents and are directed by scientists with advanced training;
- access to the laboratory is limited when work is being conducted;
- extreme precautions are taken with contaminated sharp items;
- certain procedures in which infectious aerosols or splashes may be created are conducted in biological safety cabinets or other physical containment equipment.

BIOHAZARD LEVEL 3:

Bacteria and viruses that can cause severe to fatal disease in humans, but for which vaccines or other treatments exist, such as anthrax, West Nile virus, Venezuelan equine encephalitis, SARS virus, tuberculosis, typhus, Rift Valley fever, Rocky Mountain spotted fever, yellow fever, and malaria. Among parasites *Plasmodium falciparum*, which causes malaria, and *Trypanosoma cruzi*, which causes trypanosomiasis (sleeping sickness), also come under this level.

Laboratory personnel have specific training in handling pathogenic and potentially lethal agents, and are supervised by competent scientists experienced in working with these agents. All procedures involving the manipulation of infectious materials are conducted within biological safety cabinets, specially designed hoods, or other physical containment devices, or by personnel wearing appropriate protective clothing and equipment. The laboratory has special engineering and design features.

BIOHAZARD LEVEL 4:

Viruses and bacteria that cause severe to fatal disease in humans, and for which vaccines or other treatments are not available, such as Bolivian and Argentine hemorrhagic fevers, Dengue hemorrhagic fever, Marburg virus, Ebola virus, hantaviruses, Lassa fever virus, Crimean-Congo hemorrhagic fever, and other hemorrhagic diseases. Variola virus (smallpox) is an agent that is worked with at BSL-4 despite the existence of a vaccine.

When dealing with biological hazards at this level the use of a positive-pressure personnel suit, with a segregated air supply, is mandatory. The entrance and exit of a Level Four biolab will contain multiple showers, a vacuum room, an ultraviolet-light room, autonomous detection system, and other safety precautions designed to destroy all traces of the biohazard. All air and water services going to and coming from a Biosafety Level 4 (P4) lab will undergo similar decontamination procedures to eliminate the possibility of an accidental release.



Figure: **BSL-4 hazmat suit**: A researcher in a protective suit working with the Ebola virus.

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10.3G: Finding Patient Zero and Tracking Diseases

The index case is identified in epidemiology studies by tracking down the infected patients to try to determine how the disease originated.

Learning Objectives

- Describe the concept of patient zero or the index case

Key Points

- The index or primary case is the initial patient in the population of an epidemiological investigation. It may indicate the source of the disease, the possible spread, and which reservoir holds the disease in-between outbreaks.
- In the early years of the AIDS epidemic, there was controversy about a so-called Patient Zero, who was the basis of a complex transmission scenario.
- Other prominent "Patient Zeroes" include Typhoid Mary.

Key Terms

- **"Patient Zero"**: A term used to refer to the index case in the spread of HIV in North America.
- **epidemiology**: The branch of a science dealing with the spread and control of diseases, computer viruses, concepts, etc., throughout populations or systems.

The index or primary case is the initial patient in the population of an epidemiological investigation. The index case may indicate the source of the disease, the possible spread, and which reservoir holds the disease in-between outbreaks. The index case is the first patient that indicates the existence of an outbreak. Earlier cases may be found and are labeled primary, secondary, tertiary, etc.

"Patient Zero" was used to refer to the index case in the spread of HIV in North America. The index case is identified in epidemiology studies by tracking down the infected patients to try to determine how the disease originated.

For example, in the early years of the AIDS epidemic there was controversy about a so-called Patient Zero, who was the basis of a complex transmission scenario. This epidemiological study showed how Patient Zero had infected multiple partners with HIV, and they in turn transmitted it to others and rapidly spread the virus to locations all over the world.

The CDC identified Gaëtan Dugas as the first person to bring HIV from Africa to the United States and to introduce it to gay bathhouses. Dugas was a flight attendant who was sexually promiscuous in several North American cities. He was vilified for several years as a "mass spreader" of HIV, and seen as the original source of the HIV epidemic among homosexual men. Later, the study's methodology and conclusions representation were repudiated.

A 2007 study published in the *Proceedings of the National Academy of Sciences* claimed that, based on the results of genetic analysis, current North American strains of HIV probably moved from Africa to Haiti and then entered the United States around 1969, probably through a single immigrant. However, the immigrant died in St. Louis, Missouri of complications from AIDS in 1969, and most likely became infected in the 1950s, so there were prior carriers of HIV strains in North America.

Ebola

In the eboloa outbreak of 2014, the Patient Zero was identified as a two year-old boy in Guinea who died on Dec. 2, 2013 of Ebolavirus during the fruitbat migration. His sister and mother and grandmother then died. Visitors from other villages came to pay their respects and tragically carried the virus back with them. As of November 2014, about 5,500 people had died of Ebolavirus.

Typhoid Mary

Other prominent "Patient Zeroes" include Typhoid Mary. She was the first person in the United States identified as an asymptomatic carrier of the pathogen associated with typhoid fever. She was presumed to have infected some 51 people, three of whom died, over the course of her career as a cook. She was forcibly isolated twice by public health authorities and died after a total of nearly three decades in isolation.



Figure: **Typhoid Mary poster**: Typhoid carrier. Food pollution. “In this manner the famous ‘Typhoid Mary’ infected family after family. “

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SECTION OVERVIEW

10.4: Nosocomial Infections

A nosocomial infection is an infection that is acquired in a hospital or other health care facility. To emphasize both hospital and nonhospital settings, it is sometimes instead called a health care–associated infection. Such an infection can be acquired in hospital, nursing home, rehabilitation facility, outpatient clinic, or other clinical settings. Infection is spread to the susceptible patient in the clinical setting by various means.

Topic hierarchy

10.4A: Microorganisms in the Hospital

10.4B: Compromised Host

10.4C: Chain of Transmission

10.4D: Control of Nosocomial Infections

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10.4A: Microorganisms in the Hospital

Nosocomial infections can cause severe pneumonia and infections of the urinary tract, bloodstream, and other parts of the body.

Learning Objectives

- Give examples of hospital-acquired infections (HAI) or nosocomial infections

Key Points

- Some well known nosocomial infections include: ventilator-associated pneumonia, Methicillin resistant Staphylococcus aureus, Candida albicans, Acinetobacter baumannii, Clostridium difficile, Tuberculosis, Urinary tract infection, Vancomycin-resistant Enterococcus and Legionnaires' disease.
- Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans.
- Hospital acquired pneumonia is the second most common nosocomial infection (urinary tract infection is the most common) and accounts for 15-20% of the total.

Key Terms

- **nosocomial infection**: an infection whose development is favoured by a hospital environment, such as one acquired by a patient during a hospital visit or one developing among hospital staff
- **MRSA**: Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. It is also called multidrug-resistant Staphylococcus aureus and oxacillin-resistant Staphylococcus aureus (ORSA).
- **pneumonia**: An acute or chronic inflammation of the lungs caused by viruses, bacteria or other microorganisms, or sometimes by physical or chemical irritants.
- **nosocomial**: A nosocomial infection, also known as a hospital-acquired infection or HAI, is an infection whose development is favoured by a hospital environment, such as one acquired by a patient during a hospital visit or one developing among hospital staff.

A nosocomial infection, also known as a hospital-acquired infection or HAI, is an infection whose development is favoured by a hospital environment, such as one acquired by a patient during a hospital visit, or one developed among hospital staff. Such infections include fungal and bacterial infections, and are aggravated by the reduced resistance of individual patients.

In the United States, the Centers for Disease Control and Prevention estimated roughly 1.7 million hospital-associated infections, from all types of microorganisms (including bacteria), cause or contribute to 99,000 deaths each year. In Europe, where hospital surveys have been conducted, the category of Gram-negative infections are estimated to account for two-thirds of the 25,000 deaths each year. Nosocomial infections can cause severe pneumonia and infections of the urinary tract, bloodstream, and other parts of the body. Many types are difficult to attack with antibiotics, and antibiotic resistance is spreading to Gram-negative bacteria that can infect people outside the hospital.

Known nosocomial infections include:

- Ventilator-associated pneumonia
- Staphylococcus aureus
- Methicillin resistant Staphylococcus aureus
- Candida albicans
- Pseudomonas aeruginosa
- Acinetobacter baumannii
- Stenotrophomonas maltophilia
- Clostridium difficile
- Tuberculosis
- Urinary tract infection
- Hospital-acquired pneumonia
- Gastroenteritis
- Vancomycin-resistant Enterococcus
- Legionnaires' disease.

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. It is also called multidrug-resistant Staphylococcus aureus and oxacillin-resistant Staphylococcus aureus (ORSA). MRSA is any strain of Staphylococcus aureus that has developed resistance to beta-lactam antibiotics, which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Strains unable to resist these antibiotics are classified as methicillin-sensitive Staphylococcus aureus, or MSSA. The development of such resistance does not cause the organism to be more intrinsically virulent than strains of Staphylococcus aureus that have no antibiotic resistance, but resistance does make MRSA infection more difficult to treat with standard types of antibiotics, and thus more dangerous.

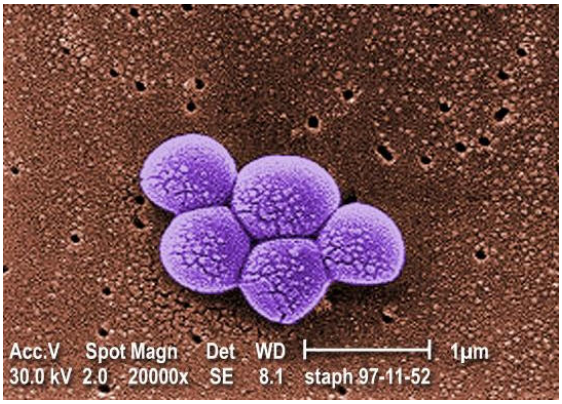

Figure: **Resistant bacterial strain**: Methicillin-resistant Staphylococcus aureus.

Hospital-acquired pneumonia (HAP), or nosocomial pneumonia, refers to any pneumonia contracted by a patient in a hospital at least 48-72 hours after being admitted. It is usually caused by a bacterial infection, rather than a virus. HAP is the second most common nosocomial infection (urinary tract infection is the most common), and accounts for 15-20% of the total. It is the most common cause of death among nosocomial infections, and is the primary cause of death in intensive care units.

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10.4B: Compromised Host

Numerous risk factors in the hospital setting can predispose a patient to infection.

Learning Objectives

- Discuss the risk factors that contribute to the acquiring of nosocomial infections or hospital-acquired infections

Key Points

- People in hospitals are usually already in a “poor state of health,” impairing their defense against bacteria.
- Invasive devices bypass the body’s natural lines of defense against pathogens and provide an easy route for infection.
- Patients’ treatments can leave them vulnerable to infection.

Key Terms

- **infection**: An uncontrolled growth of harmful microorganisms in a host.
- **defense**: The action of defending or protecting from attack, danger, or injury.
- **Invasive**: Invasive species, also called invasive exotics or simply exotics, is a nomenclature term and categorization phrase used for flora and fauna, and for specific restoration-preservation processes in native habitats, with several definitions.

Susceptible Hosts

A nosocomial infection, also known as a hospital-acquired infection or HAI, is an infection whose development is favoured by a hospital environment, such as one acquired by a patient during a hospital visit or one developing among hospital staff. Such infections include fungal and bacterial infections. They are aggravated by the reduced resistance of individual patients. Numerous risk factors in the hospital setting predispose a patient to infection. These risk factors can broadly be divided into three areas.

- People in hospitals are usually already in a ‘poor state of health’, impairing their defense against bacteria. Advanced age or premature birth, along with immunodeficiency (due to drugs, illness, or irradiation) present a general risk, while other diseases can present specific risks; for instance, chronic obstructive pulmonary disease can increase chances of respiratory tract infection.
- Invasive devices, for instance intubation tubes, catheters, surgical drains, and tracheostomy tubes all bypass the body’s natural lines of defense against pathogens and provide an easy route for infection. Patients already colonized at the time of admission are instantly put at greater risk when they undergo invasive procedures.
- Patients’ treatments can leave them vulnerable to infection: immunosuppression and antacid treatment undermine the body’s defences, while antimicrobial therapy (removing competitive flora and only leaving resistant organisms) and recurrent blood transfusions have also been identified as risk factors.

Prevention

Hospitals have sanitation protocols regarding uniforms, equipment sterilization, washing, and other preventive measures. Thorough hand washing and/or use of alcohol rubs by all medical personnel before and after each patient contact is one of the most effective ways to combat nosocomial infections. More careful use of antimicrobial agents, such as antibiotics, is also considered vital. Despite sanitation protocol, patients cannot be entirely isolated from infectious agents. Furthermore, patients are often prescribed antibiotics and other antimicrobial drugs to help treat illness; this can increase the selection pressure for the emergence of resistant strains.



Figure: **Surgical drain**: Surgical drain on the left hand after surgery of Bennet's fracture basis MTC primi manus 1. sin (S62.20) which was treated by alignment of a fracture and inside fixation by two titanium screws MS.

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10.4C: Chain of Transmission

Learning Objectives

- Differentiate between the various types of transmission: air-borne, common vehicle, vector borne, direct and indirect contact transmission

The drug-resistant Gram-negative bacteria, for the most part, threaten only hospitalized patients whose immune systems are weak. They can survive for a long time on surfaces in the hospital and they enter the body through wounds, catheters, and ventilators.

The most important and frequent mode of transmission of nosocomial infections is by direct contact. Transmission occurs when droplets containing microbes from the infected person are propelled a short distance through the air and deposited on the host's body; droplets are generated from the source person mainly by coughing, sneezing, and talking, and during the performance of certain procedures, such as bronchoscopy.

Dissemination can be either airborne droplet nuclei (small-particle residue {5 µm or smaller in size} of evaporated droplets containing microorganisms that remain suspended in the air for long periods of time) or dust particles containing the infectious agent. Microorganisms carried in this manner can be dispersed widely by air currents and may become inhaled by a susceptible host within the same room or over a longer distance from the source patient, depending on environmental factors; therefore, special air-handling and ventilation are required to prevent airborne transmission. Microorganisms transmitted by airborne transmission include Legionella, Mycobacterium tuberculosis and the rubeola and varicella viruses.

Common vehicle transmission applies to microorganisms transmitted to the host by contaminated items, such as food, water, medications, devices, and equipment. Vector borne transmission occurs when vectors such as mosquitoes, flies, rats, and other vermin transmit microorganisms.



Figure: ***Cross-transmission****: Contaminated surfaces increase cross-transmission.*

Contact transmission is divided into two subgroups: direct-contact transmission and indirect-contact transmission.

Direct-contact transmission involves a direct body surface-to-body surface contact and physical transfer of microorganisms between a susceptible host and an infected or colonized person, such as when a person turns a patient, gives a patient a bath, or performs other patient-care activities that require direct personal contact. Direct-contact transmission can also occur between two patients, with one serving as the source of the infectious microorganisms and the other as a susceptible host.

Indirect-contact transmission involves contact of a susceptible host with a contaminated intermediate object, usually inanimate, such as contaminated instruments, needles, or dressings, or contaminated gloves that are not changed between patients. In addition, the improper use of saline flush syringes, vials, and bags has been implicated in disease transmission in the US, even when healthcare workers had access to gloves, disposable needles, intravenous devices, and flushes.

Key Points

- Contact transmission is divided into two subgroups: direct-contact transmission and indirect-contact transmission.
- Direct-contact transmission involves a direct body surface-to-body surface contact and physical transfer of microorganisms.
- Indirect-contact transmission involves contact of a susceptible host with a contaminated intermediate object, usually inanimate.

Key Terms

- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.

- **susceptible**: likely to be affected by something; here, sensitive to growth inhibition by an antimicrobial drug.
- **transmission**: Transmission is the passing of a communicable disease from an infected host individual or group to a conspecific individual or group, regardless of whether the other individual was previously infected.

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10.4D: Control of Nosocomial Infections

Learning Objectives

- Give examples of ways nosocomial infections can be controlled or prevented

Hospitals have sanitation protocols regarding uniforms, equipment sterilization, washing, and other preventive measures. Thorough hand washing and/or the use of alcohol rubs by all medical personnel before and after each patient contact is one of the most effective ways to combat nosocomial infections. More careful use of antimicrobial agents, such as antibiotics, is also considered vital.

Despite sanitation protocol, patients cannot be entirely isolated from infectious agents. Furthermore, patients are often prescribed antibiotics and other antimicrobial drugs to help treat illness; this may increase the selection pressure for the emergence of resistant strains. Sterilization goes further than just sanitizing. It kills all microorganisms on equipment and surfaces through exposure to chemicals, ionizing radiation, dry heat, or steam under pressure. Isolation precautions are designed to prevent transmission of microorganisms by common routes in hospitals. Because agent and host factors are more difficult to control, interruption of transfer of microorganisms is directed primarily at transmission.

The Importance of Handwashing

Handwashing is the single most important measure to reduce the risks of transmitting skin microorganisms from one person to another or from one site to another on the same patient. Washing hands as promptly and thoroughly as possible between patient contacts and after contact with blood, body fluids, secretions, excretions, and equipment or articles contaminated by them is an important component of infection control and isolation precautions.



Figure: ***Hand washing with soap****: Handwashing is the single most important measure to reduce the risks of transmitting skin microorganisms from one person to another or from one site to another on the same patient.*

The spread of nosocomial infections among immunocompromised patients is connected with health care workers' hand contamination in almost 40% of cases. This presents a challenging problem in the modern hospitals. The best way for workers to overcome this problem is by conducting correct hand- hygiene procedures; this is why in 2005 the WHO launched the GLOBAL Patient Safety Challenge.

Two categories of micro-organisms can be present on health care workers' hands: transient flora and resident flora. The first is represented by the micro-organisms taken by workers from the environment, and the bacteria in it. These are often capable of surviving on the human skin and sometimes to grow. The second group is represented by the permanent micro-organisms living on the skin surface, on the stratum corneum or immediately under it. They are capable of surviving on the human skin and of growing freely on it. They have low pathogenicity and infection rate, and they create a kind of protection from the colonization from other more pathogenic bacteria.

The skin of workers is colonized by 3.9 x 104 – 4.6 x 106 cfu/cm2. The microbes comprising the resident flora are: Staphylococcus epidermidis, S. hominis, and Micrococcus, Propionibacterium, Corynebacterium, Dermobacterium, and Pitosporum spp., while in the transitional could be found S. aureus, and Klebsiella pneumoniae, and Acinetobacter, Enterobacter and Candida spp. The goal of hand hygiene is to eliminate the transient flora with a careful and proper performance of hand washing, using different kinds of soap, both normal and antiseptic, and alcohol-based gels. The main problems found in the practice of hand hygiene are connected with the lack of available sinks and the time-consuming performance of hand washing. An easy way to resolve this problem could be the use of alcohol-based hand rubs, because of faster application compared to correct hand washing.

The Second Line of Defense: Gloves

Gloves play an important role in reducing the risks of transmission of microorganisms. Gloves are worn for three important reasons in hospitals.

- They are worn to provide a protective barrier and to prevent gross contamination of the hands when touching blood, body fluids, secretions, excretions, mucous membranes, and non-intact skin. In the USA, the Occupational Safety and Health Administration (OSHA) has mandated wearing gloves to reduce the risk of blood-borne pathogen infections.
- Gloves are worn to reduce the likelihood microorganisms present on the hands of personnel will be transmitted to patients during invasive or other patient-care procedures that involve touching a patient's mucous membranes and nonintact skin.
- They are worn to reduce the likelihood the hands of personnel contaminated with micro-organisms from a patient or a fomite (contaminated object) can be transmitted to another patient. In this situation, gloves must be changed between patient contacts, and hands should be washed after gloves are removed.

Surfaces

Sanitizing surfaces is an often overlooked, yet crucial, component of the strategy for the cycle of infection in health care environments. Modern sanitizing methods such as NAV-CO2 have been effective against gastroenteritis, MRSA, and influenza agents. Use of hydrogen peroxide vapor has been clinically proven to reduce infection rates and risk of acquisition. Hydrogen peroxide is effective against endospore-forming bacteria, such as Clostridium difficile, where alcohol has been shown to be ineffective.

Microorganisms are known to survive on inanimate "touch" surfaces for extended periods of time. This can be especially troublesome in hospital environments, where patients with immunodeficiencies are at enhanced risk for contracting nosocomial infections.

Wearing an apron during patient care reduces the risk of infection. The apron should either be disposable or be used only when caring for a specific patient.

Key Points

- Handwashing frequently is called the single most important measure to reduce the risks of transmitting skin microorganisms from one person to another or from one site to another on the same patient.
- Thorough hand washing and/or use of alcohol rubs by all medical personnel before and after each patient contact is one of the most effective ways to combat nosocomial infections.
- Sanitizing surfaces is an often overlooked, yet crucial, component of breaking the cycle of infection in health care environments.

Key Terms

- **sterilization**: Any process that eliminates or kills all forms of microbial life present on a surface, solution, or solid compound.
- **nosocomial**: contracted in a hospital, or arising from hospital treatment
- **sanitation**: The policy and practice of protecting health through hygienic measures.

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SECTION OVERVIEW

10.5: Epidemiology and Public Health

Epidemiology is the study and analysis of the distribution (who, when, and where) and determinants of health and disease conditions in defined populations.

Topic hierarchy

10.5A: Descriptive Epidemiology

10.5B: Analytical Epidemiology

10.5C: Experimental Epidemiology

10.5D: Public Health Measures for Disease Control

10.5E: Global Health

10.5F: Emerging and Reemerging Infectious Diseases

10.5G: Biological Weapons

10.5H: Technology and New Infectious Agents

10.5I: Current Epidemics

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10.5A: Descriptive Epidemiology

Descriptive epidemiology focuses on describing disease distribution by characteristics relating to time, place, and people.

Learning Objectives

- Describe the role of a descriptive epidemiology

Key Points

- Epidemiology is the science concerned with the study of the factors that influence and determine the frequency and distribution of disease, injury, and other health -related events and their causes in a defined human population.
- The more fully a descriptive epidemiologist can describe people, places and times, and any correlations between the three, the more likely it is that patterns will emerge which can be considered as risk factors for certain kinds of health issues.
- Epidemiologists use data as an information source for communicating information to people and to influence public policy.

Key Terms

- **socioeconomic**: Of or pertaining to social and economic factors.
- **epidemiology**: The branch of a science dealing with the spread and control of diseases, computer viruses, concepts, etc., throughout populations or systems.
- **risk factor**: A variable associated with an increased risk of disease or infection.

The goal of epidemiology is to establish causal factors for health issues in order to improve the health and safety of entire populations. A population can refer to a town, country, age group, or race. Health issues refer to anything that might impact health in the present or future. For epidemiologists, data on who is most likely to be injured in car crashes can be just as valuable as a topic of inquiry as data on what part of the population is most at risk for developing complications from the flu. In order to accomplish this, epidemiology has two main branches: descriptive and analytical.

Descriptive epidemiology evaluates and catalogs all the circumstances surrounding a person affected by a health event of interest. Analytical epidemiologists use data gathered by descriptive epidemiology experts to look for patterns suggesting causation. The end goal of both branches is to reduce the incidence of health events or diseases by understanding the risk factors for the health events or diseases. Both descriptive and analytical epidemiology often serve public health organizations by providing information that may reduce disease or reduce other kinds of events that impact people's health.

The primary considerations for descriptive epidemiology are frequency and pattern. Frequency evaluates the rate of occurrence, and pattern helps analytical epidemiologists suggest risk factors. Descriptive epidemiology evaluates frequency and pattern by examining the person, place, and time in relationship to health events.

Descriptive epidemiology examines factors like age, education, socioeconomic status, availability of health services, race, and gender. Evaluations of specific individuals may also include gathering information on behaviors like drug abuse, shift work, eating, and exercise patterns.

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10.5B: Analytical Epidemiology

Epidemiology draws statistical inferences, mostly about causes of disease in populations based on available samples of it.

Learning Objectives

- Describe the role of an analytical epidemiologist

Key Points

- Epidemiologists employ a range of study designs from the observational to experimental and they are generally categorized as descriptive, analytic, and experimental.
- Analytic epidemiology aims to further examine known associations or hypothesized relationships.
- Analytical observations deal more with the 'how' of a health -related event.

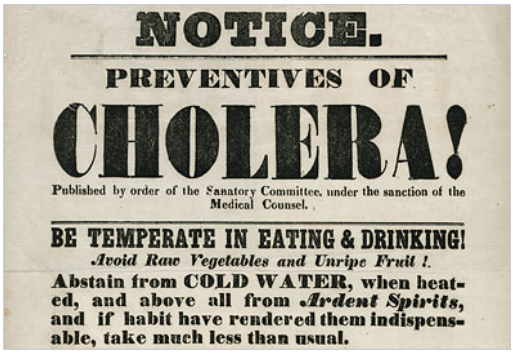
Key Terms

- **analytical**: pertaining to or emanating from analysis.
- **epidemiology**: Epidemiology is the study (or the science of the study) of the patterns, causes, and effects of health and disease conditions in defined populations.

Epidemiology is the study (or the science of the study) of the patterns, causes, and effects of health and disease conditions in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results (including peer review and occasional systematic review). Epidemiology has helped develop methodology used in clinical research, public health studies and, to some extent, basic research in the biological sciences.

Epidemiologists employ a range of study designs from observational to experimental and generally categorized as descriptive, analytic (aiming to further examine known associations or hypothesized relationships), and experimental (a term often equated with clinical or community trials of treatments and other interventions).

Where descriptive epidemiology describes occurrence of disease (or of its determinants) within a population, the analytical epidemiology aims to gain knowledge on the quality and the amount of influence that determinants have on the occurrence of disease. The usual way to gain this knowledge is by group comparisons. Such a comparison starts from one or more hypotheses about how the determinant may influence occurrence of disease. Analytical epidemiology attempts to determine the cause of an outbreak. Using the case control method, the epidemiologist can look for factors that might have preceded the disease. Often, this entails comparing a group of people who have the disease with a group that is similar in age, sex, socioeconomic status, and other variables, but does not have the disease. In this way, other possible factors, e.g., genetic or environmental, might be identified as factors related to the outbreak.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PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit!.

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

Figure: **Cholera Outbreak**: The outdated public health advice demonstrates the lack of understanding of the disease and its actual causative factors in the absence of epidemiological analysis.

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10.5C: Experimental Epidemiology

Experimental epidemiology uses an experimental model to confirm a causal relationship suggested by observational studies.

Learning Objectives

- Summarize the purpose of experimental epidemiology and the three case types: randomized control, field and community trial

Key Points

- Experimental epidemiology is the study of the relationships of various factors determining the frequency and distribution of diseases in a community.
- Experimental epidemiology contains three case types: randomized control trial (often used for new medicine or drug testing), field trial (conducted on those at a high risk of conducting a disease), and community trial (research on social originating diseases).
- The method employs prospective population experiments designed to test epidemiological hypotheses, and usually attempt to relate the postulated cause to the observed effect. Trials of new anthelmintics are an example.

Key Terms

- **epidemiology**: Epidemiology is the study (or the science of the study) of the patterns, causes, and effects of health and disease conditions in defined populations.
- **Experimental**: An experiment is a methodical procedure carried out with the goal of verifying, falsifying, or establishing the validity of a hypothesis.
- **statistical**: of or pertaining to statistics

Epidemiology is the study (or the science of the study) of the patterns, causes, and effects of health and disease conditions in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results (including peer review and occasional systematic review). Epidemiology has helped develop methodology used in clinical research, public health studies and, to a lesser extent, basic research in the biological sciences.



Figure: **Early epidemiology**: Original map by John Snow showing the clusters of cholera cases in the London epidemic of 1854. John Snow's investigative work was one of the first examples of epidemiology. He discovered that families that drew their water from the Broad St well became infected with cholera.

Epidemiologists employ a range of study designs from the observational to experimental and they are generally categorized as descriptive, analytic (aiming to further examine known associations or hypothesized relationships), and experimental (a term often equated with clinical or community trials of treatments and other interventions). In observational studies, nature is allowed to "take its course", as epidemiologists observe from the sidelines. Controversially, in experimental studies, the epidemiologist is the one in control of all of the factors entering a certain case study. Epidemiological studies are aimed, where possible, at revealing unbiased

relationships between exposures such as alcohol or smoking, biological agents, stress, or chemicals to mortality or morbidity. The identification of causal relationships between these exposures and outcomes is an important aspect of epidemiology. Modern epidemiologists use informatics as a tool.

Experimental epidemiology contains three case types: randomized control trial (often used for new medicine or drug testing), field trial (conducted on those at a high risk of conducting a disease), and community trial (research on social originating diseases). Experimental epidemiology tests a hypothesis about a disease or disease treatment in a group of people. This strategy might be used to test whether or not a particular antibiotic is effective against a particular disease-causing organism. One group of infected individuals is divided randomly so that some receive the antibiotic and others receive a placebo—a “false” drug that is not known to have any medical effect. In this case, the antibiotic is the variable, i.e., the experimental factor being tested to see if it makes a difference between the two otherwise similar groups. If people in the group receiving the antibiotic recover more rapidly than those in the other group, it may logically be concluded that the variable—antibiotic treatment—made the difference. Thus, the antibiotic is said to be effective.

Although epidemiology is sometimes viewed as a collection of statistical tools used to elucidate the associations of exposures to health outcomes, a deeper understanding of this science is that of discovering causal relationships.

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10.5D: Public Health Measures for Disease Control

Promotion of hand washing, breastfeeding, delivery of vaccinations, and distribution of condoms are examples of public health measures.

Learning Objectives

- Give examples of common public health measures that are recommended to control the spread of disease

Key Points

- Hand washing for hand hygiene is the act of cleaning the hands with or without the use of water or another liquid, or with the use of soap, for the purpose of removing soil, dirt, and/or microorganisms.
- Breastfeeding is the feeding of an infant or young child with breast milk directly from female human breasts (i.e., via lactation) rather than from a baby bottle or other container.
- Vaccination is the administration of antigenic material (a vaccine) to stimulate an individual's immune system to develop adaptive immunity to a pathogen.

Key Terms

- **hygiene**: Those conditions and practices that promote and preserve health.
- **immunity**: the state of being insusceptible to a specific thing.
- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.

Public Health Measures

The focus of public health intervention is to improve health and quality of life through the prevention and treatment of disease and other physical and mental health conditions. This can be done through surveillance of cases, and the promotion of healthy behaviors. Promotion of hand washing and breastfeeding, delivery of vaccinations, and distribution of condoms to control the spread of sexually transmitted diseases, are examples of common public health measures.

HAND WASHING

Hand washing for hand hygiene is the act of cleaning the hands with or without the use of water or another liquid, or with the use of soap, for the purpose of removing soil, dirt, and/or microorganisms. Medical hand hygiene pertains to the hygiene practices related to the administration of medicine and medical care that prevents or minimizes disease and the spreading of disease. The main medical purpose of washing hands is to cleanse the hands of pathogens (including bacteria or viruses) and chemicals, which can cause personal harm or disease. This is especially important for people who handle food or work in the medical field, but it is also an important practice for the general public. People can become infected with respiratory illnesses, such as influenza or the common cold; for example, if they don't wash their hands before touching their eyes, nose, or mouth. Indeed, the Centers for Disease Control and Prevention (CDC) has stated: "It is well documented that one of the most important measures for preventing the spread of pathogens is effective hand washing. "



Figure: **Hand Cleaning Station**: A hand cleaning station at the entrance of the Toronto General Hospital

As a general rule, however, handwashing protects people poorly or not at all from droplet- and airborne diseases, such as measles, chickenpox, influenza, and tuberculosis. It protects best against diseases transmitted through fecal-oral routes (such as many forms of stomach flu) and direct physical contact (such as impetigo). In addition to hand washing with soap and water, the use of alcohol

gels is another form of killing some kinds of pathogens and healthful bacteria, but their effectiveness is disputed, and may lead to antibiotica-resistant bacterial strains.

BREASTFEEDING

Breastfeeding is the feeding of an infant or young child with breast milk directly from female human breasts (i.e., via lactation) rather than from a baby bottle or other container. Babies have a sucking reflex that enables them to suck and swallow milk. It is recommended that mothers breastfeed for six months or more, without the addition of infant formula or solid food. After the addition of solid food, mothers are advised to continue breastfeeding for at least a year, and can continue for two years or more. Human breast milk is the healthiest form of milk for babies. There are few exceptions, such as when the mother is taking certain drugs or is infected with human T-lymphotropic virus, or has active untreated tuberculosis. Maternal HIV infection is always an absolute contraindication to breastfeeding in developed countries with access to infant formula and clean drinking water (regardless of maternal HIV viral load or antiretroviral treatment) due to the risk for mother to child HIV transmission. Breastfeeding promotes health and helps to prevent disease. Artificial feeding is associated with more deaths from diarrhea in infants in both developing and developed countries. Experts agree that breastfeeding is beneficial, and have concerns about artificial formulas but there are conflicting views about how long exclusive breastfeeding remains beneficial.

VACCINATION

Vaccination is the administration of antigenic material (a vaccine) to stimulate an individual's immune system to develop adaptive immunity to a pathogen. Vaccines can prevent or ameliorate morbidity from infection. The effectiveness of vaccination has been widely studied and verified; for example, the influenza vaccine, the HPV vaccine, and the chicken pox vaccine. Vaccination is the most effective method of preventing infectious diseases; widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the restriction of diseases such as polio, measles, and tetanus from much of the world.

CONDOMS

A condom is a barrier device commonly used during sexual intercourse to reduce the probability of pregnancy and spreading sexually transmitted diseases. It is put on a man's erect penis and physically blocks ejaculated semen from entering the body of a sexual partner. Condoms are also used for collection of semen for use in infertility treatment. In the modern age, condoms are most often made from latex, but some are made from other materials such as polyurethane, polyisoprene, or lamb intestine. A female condom is also available, often made of nitrile.

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10.5E: Global Health

Global health is the health of populations in a global context and transcends the perspectives and concerns of individual nations.

Learning Objectives

- Outline the various perspectives that provide the framework for global health initiatives: epidemiological, medical, economic and political approaches

Key Points

- Health problems that transcend national borders or have a global political and economic impact are often emphasized.
- The major international agency for health is the World Health Organization (WHO). Other important agencies with impact on global health activities include UNICEF, World Food Programme (WFP), United Nations University – International Institute for Global Health, and the World Bank.
- Global health is a research field at the intersection of medical and social science disciplines, such as demography, economics, epidemiology, political economy and sociology.

Key Terms

- **health**: The state of being free from physical or psychological disease, illness, or malfunction; wellness.
- **populations**: A population is all the organisms that both belong to the same group or species and live in the same geographical area.
- **nations**: A nation may refer to a community of people who share a common language, culture, ethnicity, descent, or history. In this definition, a nation has no physical borders.

Global Health

Global health is the health of populations in a global context and transcends the perspectives and concerns of individual nations. Health problems that transcend national borders or have a global political and economic impact are often emphasized. It has been defined as “the area of study, research and practice that places a priority on improving health and achieving equity in health for all people worldwide. ” Thus, global health is about worldwide improvement of health, reduction of disparities, and protection against global threats that disregard national borders. The application of these principles to the domain of mental health is called global mental health.

The major international agency for health is the World Health Organization (WHO). Other important agencies with impact on global health activities include UNICEF, World Food Programme (WFP), United Nations University – International Institute for Global Health, and the World Bank. A major initiative for improved global health is the United Nations Millennium Declaration and the globally endorsed Millennium Development Goals.



Figure: **Flag of the World Health Organization**: This is the flag of the World Health Organization.

Global health is a research field at the intersection of medical and social science disciplines, such as demography, economics, epidemiology, political economy, and sociology. Through these different disciplinary perspectives, it focuses on determinants and the distribution of health in international contexts.

Global Health Perspectives

An epidemiological perspective identifies major global health problems. A medical perspective describes the pathology of major diseases, and promotes prevention, diagnosis, and treatment of these diseases.

An economic perspective emphasizes the cost-effectiveness and cost-benefit approaches for both individual and population health allocation. Aggregate analysis focuses on analysis for the health sector. For instance, governments and non-governmental organizations (NGOs) may engage in aggregate analysis.

Cost-effectiveness analysis compares the costs and health effects of an intervention to assess whether health investments are worthwhile from an economic perspective. It is necessary to distinguish between independent interventions and mutually exclusive interventions. For independent interventions, average cost-effectiveness ratios suffice. However, when mutually exclusive interventions are compared, it is essential to use incremental cost-effectiveness ratios. The latter comparisons suggest how to achieve maximal health care effects with the available resources.

Another ethical approach emphasizes distributional considerations. The Rule of Rescue, coined by A.R. Jonsen (1986), is one way to address distributional issues. This rule specifies that it is “a perceived duty to save endangered life where possible. ” John Rawls ideas on impartial justice is a contractual perspective on distribution. These ideas have been applied by Amartya Sen to address key aspects of health equity. Bioethics research also examines international obligations of justice, in three broadly clustered areas: When are international inequalities in health unjust? Where do international health inequalities come from? How do we meet health needs justly if we can’t meet them all?

A political approach emphasizes political economy considerations applied to global health. Political economy originally was the term for studying production, buying and selling, and their relations with law, custom, and government. Originating in moral philosophy (e.g., Adam Smith was professor of Moral Philosophy at the University of Glasgow), political economy of health is the study of how economies of states influence aggregate population health outcomes.

There are many perspectives and approaches to take when it comes to issues of global health, hence why the global health system is still struggling. Some perceive the immunization and prevention of disease to be a form of public democracy, others view it as a moral duty or an investment in self-protection. The journalist, Laurie Garrett explores the various perspectives shaping global health and suggests that it is due to perspective divergence that is hindering monetary funding and philanthropic efforts of organizations to properly control disease.

There are dangers to having divergent perspectives especially if it is a biased one; such as exemplified by Andrew Natsios of USAID, when he proclaimed that antiretrovirals should not be distributed to HIV-stricken Africa due to the occupants lacking a concept of time and clocks to properly facilitate the proper sequence of drug consumption. In addition, divergent perspectives can lead to “stove-piping”, which localizes funding to only specific causes while neglecting the larger and more important issues. The most important aspect in achieving global health is to take on a research approach and act accordingly to data and proven research because global health needs to be focused on as a whole, rather than specific causes.

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10.5F: Emerging and Reemerging Infectious Diseases

An emerging infectious disease is a disease with a rate of incidence that has increased in the past 20 years, and could increase in the near future.

Learning Objectives

- Give examples of emerging and remerging infectious diseases

Key Points

- Emerging infections account for at least 12% of all human pathogens.
- Emerging infections deseases are caused by newly identified species or strains that may have evolved from a known infection or spread to a new population or area undergoing ecologic transformation, or be reemerging infections, such as drug resistant tuberculosis.
- Adverse synergistic interactions between emerging diseases and other infectious and non-infectious conditions leading to the development of novel syndemics are of growing concern.

Key Terms

- **emerging infectious disease**: An emerging infectious disease (EID) is an infectious disease with an incidence rate that has increased in the past 20 years and could increase in the near future. Emerging infections account for at least 12% of all human pathogens.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.
- **species**: In biology, a species is one of the basic units of biological classification and a taxonomic rank. A species is often defined as a group of organisms capable of interbreeding and producing fertile offspring.

An emerging infectious disease (EID) is an infectious disease whose incidence has increased in the past 20 years, and could increase in the near future. Emerging infections account for at least 12% of all human pathogens. EIDs are caused by newly identified species or strains (e.g., SARS, AIDS) that may have evolved from a known infection (e.g., influenza), or spread to a new population (e.g., West Nile virus), or to an area undergoing ecologic transformation (e.g., Lyme disease). They could also be reemerging infections, such as drug resistant tuberculosis. Of growing concern are adverse synergistic interactions between emerging diseases and other infectious and non-infectious conditions leading to the development of novel syndemics.

SARS

Severe acute respiratory syndrome (SARS) is a viral respiratory disease in humans which is caused by the SARS coronavirus (SARS-CoV). Between November 2002 and July 2003, an outbreak of SARS in Hong Kong nearly became a pandemic, with 8,422 cases and 916 deaths worldwide (10.9% fatality), according to the World Health Organization (WHO). Within weeks, SARS spread from Hong Kong to infect individuals in 37 countries. The last infected human case of the outbreak occurred in June 2003, and there was a laboratory-induced infection case in 2004. SARS is not claimed to have been eradicated (unlike smallpox), as it may still be present in its natural host reservoirs (animal populations) and may return to the human population. During the outbreak, the fatality of SARS was less than 1% for people aged 24 or younger, 6% for those 25 to 44, 15% for those 45 to 64, and more than 50% for those over 65. For comparison, the fatality of influenza is usually under 0.03% (primarily among the elderly), but rose to 2% during the most severe pandemic to date.

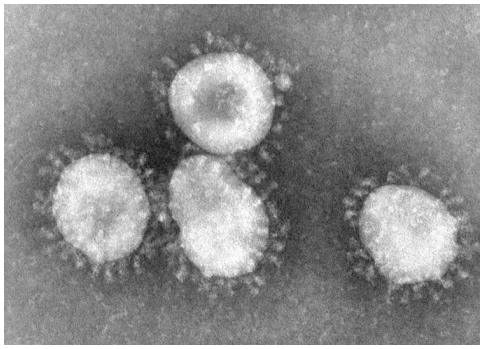

Figure: **Coronaviruses**: Coronaviruses are a group of viruses that have a halo, or crown-like (corona) appearance when viewed under an electron microscope. If you have a cold 10-15% of the time it is caused by a virus like this.

HIV

Human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). During the initial infection a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses it interferes more and more with the immune system, making people much more likely to get infections, including opportunistic infections, and tumors that do not usually affect people with working immune systems.

Influenza

Influenza, commonly known as the flu, is an infectious disease of birds and mammals caused by RNA viruses of the family Orthomyxoviridae, the influenza viruses. The most common symptoms are chills, fever, sore throat, muscle pains, headache (often severe), coughing, weakness/fatigue and general discomfort. Although it is often confused with other influenza-like illnesses, especially the common cold, influenza is a more severe disease caused by a different type of virus. Influenza may produce nausea and vomiting, particularly in children, but these symptoms are more common in the unrelated gastroenteritis, which is sometimes inaccurately referred to as “stomach flu” or “24-hour flu. ”

West Nile Virus

West Nile virus (WNV) is a mosquito-borne zoonotic arbovirus belonging to the genus flavivirus in the family flaviviridae. This flavivirus is found in temperate and tropical regions of the world. It was first identified in the West Nile subregion in the East African nation of Uganda in 1937. Prior to the mid 1990s, WNV disease occurred only sporadically and was considered a minor risk for humans. However, there was an outbreak in Algeria in 1994, with cases of WNV-caused encephalitis, and the first large outbreak in Romania in 1996, with a high number of cases with neuroinvasive disease. WNV has now spread globally, with the first case in the Western Hemisphere being identified in New York City in 1999; over the next 5 years, the virus spread across the continental United States, north into Canada, and southward into the Caribbean Islands and Latin America. WNV also spread to Europe, beyond the Mediterranean Basin. A new strain of the virus was recently (2012) identified in Italy. WNV is now considered to be an endemic pathogen in Africa, Asia, Australia, the Middle East, Europe and in the United States, which in 2012 has experienced one of its worst epidemics.

Tuberculosis

Tuberculosis, MTB, or TB (short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected.

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10.5G: Biological Weapons

Biological warfare (BW) is the use of biological toxins or infectious agents with the intent to kill or incapacitate.

Learning Objectives

- Recognize the characteristics of biological weapons

Key Points

- Biological weapons (often termed “bio-weapons”, “biological threat agents”, or “bio-agents”) are living organisms or replicating entities (viruses) that reproduce or replicate within their host victims.
- Biological weapons may be employed in various ways to gain a strategic or tactical advantage over an adversary, either by threats or by actual deployments.
- As a tactical weapon for military use, a significant problem with a BW attack is that it would take days to be effective, and therefore might not immediately stop an opposing force.

Key Terms

- **Biological warfare**: Biological warfare (BW) — also known as germ warfare — is the use of biological toxins or infectious agents such as bacteria, viruses, and fungi with the intent to kill or incapacitate humans, animals, or plants as an act of war.
- **psychochemical weapon**: Agents used within the context of military aggression.

Biological warfare (BW) — also known as germ warfare — is the use of biological toxins or infectious agents such as bacteria, viruses, and fungi with the intent to kill or incapacitate humans, animals, or plants as an act of war. Biological weapons (often termed “bio-weapons”, “biological threat agents”, or “bio-agents”) are living organisms or replicating entities (viruses) that reproduce or replicate within their host victims. Entomological (insect) warfare is also considered a type of BW.

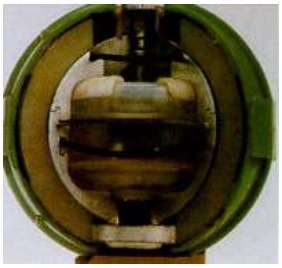

Figure: **Biological Bomblet**: The E120 biological bomblet was one of a number of spherical biological bomblets that were developed before the United States discontinued its offensive program in the 1970s. The vaned outer shell of this spherical bomblet was designed to provide rotation during flight. On impact, the outer shell would shatter; the bomblet was asymmetrically weighted so that agent would then be sprayed from the top of the bomblet. The E120 bomblet was developed in the early 1960s. Its 11.4 cm diameter carried 0.1 kg of liquid biological agent.

Biological weapons may be employed in various ways to gain a strategic or tactical advantage over an adversary, either by threats or by actual deployments. Like some chemical weapons, biological weapons may also be useful as area denial weapons. These agents may be lethal or non-lethal, and may be targeted against a single individual, a group of people, or even an entire population. They may be developed, acquired, stockpiled, or deployed by nation states or by non-national groups. In the latter case, or if a nation-state uses it clandestinely, it may also be considered bioterrorism.

There is an overlap between BW and chemical warfare, as the use of toxins produced by living organisms is considered under the provisions of both the Biological Weapons Convention and the Chemical Weapons Convention. Toxins and psychochemical weapons are often referred to as midspectrum agents. Unlike bioweapons, these midspectrum agents do not reproduce in their host and are typically characterized by shorter incubation periods.

Offensive biological warfare, including the mass production, stockpiling, and use of biological weapons, was outlawed by the 1972 Biological Weapons Convention (BWC). The rationale behind this treaty, which has been ratified or acceded to by 165 countries as of 2011, is to prevent a biological attack which could conceivably result in large numbers of civilian fatalities and cause severe disruption to economic and societal infrastructure. Many countries, including signatories of the BWC, currently pursue research into the defense or protection against BW, which is not prohibited by the BWC.

A nation or group that can pose a credible threat of mass casualty has the ability to alter the terms on which other nations or groups interact with it. Biological weapons allow for the potential to create a level of destruction and loss of life far in excess of nuclear, chemical, or conventional weapons, relative to their mass and cost of development and storage. Therefore, biological agents may be useful as strategic deterrents in addition to their utility as offensive weapons on the battlefield.

As a tactical weapon for military use, a significant problem with a BW attack is that it would take days to be effective, and therefore might not immediately stop an opposing force. Some biological agents (especially smallpox, plague, and tularemia) have the capability of person-to-person transmission via aerosolized respiratory droplets. This feature can be undesirable, as the agent or agents may be transmitted by this mechanism to unintended populations, including neutral or even friendly forces. While containment of BW is less of a concern for certain criminal or terrorist organizations, it remains a significant concern for the military and civilian populations of virtually all nations.

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10.5H: Technology and New Infectious Agents

Technology aids in the identification of new infectious agents, but it also contributes to the emergence of new diseases.

Learning Objectives

- Give examples demonstrating the positive and negative impacts technology has had on new infectious agents

Key Points

- Advanced technology enables rapid identification of pathogens causing disease outbreaks and helps accelerate treatment strategies.
- The effect of new technology on the environment is related to the emergence of many new infectious diseases.
- Infectious diseases are sometimes called ” contagious ” when they are easily transmitted by contact with an ill person or their secretions (e.g., influenza).

Key Terms

- **infectious**: Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.

Technology: The Good

The use of advanced technology and molecular methods for detection, identification, and characterization of infectious agents is gaining importance in clinical microbiology laboratories. Emerging and re-emerging pathogens pose several challenges to diagnosis, treatment, and public health surveillance. Identification of an emerging pathogen by conventional methods is difficult and time-consuming due to the ‘novel’ nature of the agent. Identification requires a large array of techniques including cell cultures, inoculation of animals, cultivation using artificial media, histopathological evaluation of tissues (if available), and serological techniques using surrogate antigens.

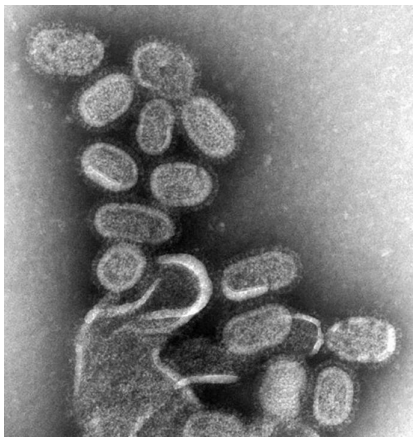

Figure: **Influenza**: TEM of negatively stained influenza virions, magnified approximately 100,000 times. Modern transport contributes in spreading diseases faster.

Looking back at past epidemics or outbreaks caused by previously unknown infectious agents, we realize that identification and characterization of a new infectious agent can take years, decades, or even centuries. Such time frames have been decreased to weeks or months by the use of powerful molecular techniques, as seen with the identification of severe acute respiratory syndrome coronavirus (SARS-CoV) within weeks of the first cases reported, the discovery of a new hantavirus in North America in 1993, and the detection of bacteria as etiological pathogens of human infections such as *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum* in human monocytotropic ehrlichiosis and human granulocytotropic anaplasmosis, respectively.

Molecular techniques offer several advantages over conventional methods, including high sensitivity and specificity, speed, ease of standardization, and automation. Other advantages include identification of novel, non-cultivable or very slowly growing organisms, strain typing in epidemiological studies, antimicrobial susceptibility determination, and monitoring treatment by measuring bacterial or viral loads.

Technology: The Bad

The effects of new technology on the environment are related to the emergence of many infectious diseases. For example, Lyme disease, hantavirus pulmonary syndrome (HPS), and Lassa fever all emerged when humans began encountering the insect vector (for Lyme disease) or rodent host (for HPS and Lassa fever) of the causative agents in greater numbers than ever before. Factors related to the emergence of infectious diseases such as Legionnaire disease and hemolytic uremic syndrome include changing technologies: air conditioning systems and mass food production, respectively.

Technology: The Ugly

Several human activities have led to the emergence and spread of new diseases:

ENCROACHMENT ON WILDLIFE HABITATS

The construction of new villages and housing developments in rural areas forces animals to live in dense populations, creating opportunities for microbes to mutate and emerge.

CHANGES IN AGRICULTURE

The introduction of new crops attracts new crop pests and the microbes they carry to farming communities, exposing people to unfamiliar diseases.

DESTRUCTION OF RAIN FORESTS

As countries make use of their rain forests by building roads and clearing areas for settlement or commercial ventures, people encounter insects and other animals harboring previously unknown microorganisms.

UNCONTROLLED URBANIZATION

The rapid growth of cities in many developing countries tends to concentrate large numbers of people into crowded areas with poor sanitation. These conditions foster transmission of contagious diseases.

MODERN TRANSPORT

Ships and other cargo carriers often harbor unintended ‘passengers’ that can spread diseases to faraway destinations. With international air travel, people infected with a disease can carry it to distant lands, or home to their families, before their first symptoms appear.

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10.5I: Current Epidemics

An epidemic occurs when new cases of a disease, in a given human population, and during a given period, substantially exceed expectations.

Learning Objectives

- Give examples of current epidemics

Key Points

- Epidemiologists often consider the term outbreak to be synonymous to epidemic, but the general public typically perceives outbreaks to be more local and less serious than epidemics.
- Epidemics of infectious disease are generally caused by a change in the ecology of the host population (e.g. increased stress or increase in the density of a vector species), a genetic change in the parasite population or the introduction of a new parasite to a host population.
- In the 20th century three influenza pandemics occurred, each caused by the appearance of a new strain of the virus in humans, and killed tens of millions of people.

Key Terms

- **epidemic**: A widespread disease that affects many individuals in a population.
- **population**: A collection of organisms of a particular species, sharing a particular characteristic of interest, most often that of living in a given area.
- **infectious**: Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism.

Epidemics

In epidemiology, an epidemic occurs when new cases of a certain disease, in a given human population, and during a given period, substantially exceed what is expected based on recent experience. Epidemiologists often consider the term outbreak to be synonymous to epidemic, but the general public typically perceives outbreaks to be more local and less serious than epidemics.

CAUSES

Epidemics of infectious disease are generally caused by a change in the ecology of the host population (e.g. increased stress or increase in the density of a vector species), a genetic change in the parasite population or the introduction of a new parasite to a host population (by movement of parasites or hosts). Generally, an epidemic occurs when host immunity to a parasite population is suddenly reduced below that found in the endemic equilibrium and the transmission threshold is exceeded.

EPIDEMIC VS. PANDEMIC

An epidemic may be restricted to one location; however, if it spreads to other countries or continents and affects a substantial number of people, it may be termed a *pandemic*. The declaration of an epidemic usually requires a good understanding of a baseline rate of incidence; epidemics for certain diseases, such as influenza, are defined as reaching some defined increase in incidence above this baseline. A few cases of a very rare disease may be classified as an epidemic, while many cases of a common disease (such as the common cold) would not.

INFLUENZA EPIDEMICS

Influenza is an infectious disease of birds and mammals caused by RNA viruses of the family Orthomyxoviridae, the influenza viruses. The most common symptoms are chills, fever, sore throat, muscle pains, headache (often severe), coughing, weakness/fatigue and general discomfort. Although it is often confused with other influenza-like illnesses, especially the common cold, influenza is a more severe disease caused by a different type of virus. Influenza may produce nausea and vomiting, particularly in children, but these symptoms are more common in the unrelated gastroenteritis, which is sometimes inaccurately referred to as “stomach flu” or “24-hour flu”.

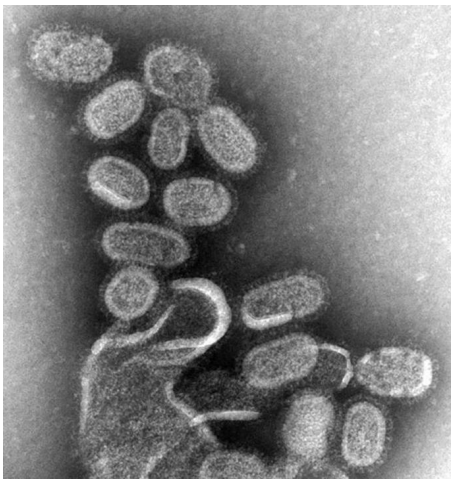

Figure: **Influenza**: TEM of negatively stained influenza virions, magnified approximately 100,000 times. Modern transport contributes in spreading diseases faster.

Typically, influenza is transmitted through the air by coughs or sneezes, creating aerosols containing the virus. Influenza can also be transmitted by direct contact with bird droppings or nasal secretions, or through contact with contaminated surfaces. Airborne aerosols have been thought to cause most infections, although which means of transmission is most important is not absolutely clear. Influenza viruses can be inactivated by sunlight, disinfectants and detergents. As the virus can be inactivated by soap, frequent hand washing reduces the risk of infection.

Influenza spreads around the world in seasonal epidemics, resulting in about three to five million yearly cases of severe illness and about 250,000 to 500,000 yearly deaths, rising to millions in some pandemic years.

In the 20th century three influenza pandemics occurred, each caused by the appearance of a new strain of the virus in humans, and killed tens of millions of people. Often, new influenza strains appear when an existing flu virus spreads to humans from another animal species, or when an existing human strain picks up new genes from a virus that usually infects birds or pigs. An avian strain named H5N1 raised the concern of a new influenza pandemic after it emerged in Asia in the 1990s, but it has not evolved to a form that spreads easily between people.

In April 2009 a novel flu strain evolved that combined genes from human, pig, and bird flu. Initially dubbed “swine flu” and also known as influenza A/H1N1, it emerged in Mexico, the United States, and several other nations. The World Health Organization officially declared the outbreak to be a pandemic level 6 on 11 June 2009. However, the WHO’s declaration of a pandemic level 6 was an indication of spread, not severity; the strain actually having a lower mortality rate than common flu outbreaks.

VACCINATIONS

Vaccinations against influenza are usually made available to people in developed countries. Farmed poultry is often vaccinated to avoid decimation of the flocks. The most common human vaccine is the trivalent influenza vaccine (TIV) that contains purified and inactivated antigens against three viral strains. Typically, this vaccine includes material from two influenza A virus subtypes and one influenza B virus strain. The TIV carries no risk of transmitting the disease, and it has very low reactivity. A vaccine formulated for one year may be ineffective in the following year, since the influenza virus evolves rapidly, and new strains quickly replace the older ones.

Antiviral drugs such as the neuraminidase inhibitor oseltamivir (Tamiflu) have been used to treat influenza; however, their effectiveness is difficult to determine due to much of the data remaining unpublished.

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CHAPTER OVERVIEW

11: Immunology

Immunology is a branch of biology that covers the study of immune systems in all organisms. Immunology charts, measures, and contextualizes the: physiological functioning of the immune system in states of both health and diseases; malfunctions of the immune system in immunological disorders (such as autoimmune diseases, hypersensitivities, immune deficiency, and transplant rejection); the physical, chemical and physiological characteristics of the components of the immune system *in vitro*, *in situ*, and *in vivo*.

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Thumbnail: Scanning electron micrograph of a phagocyte (yellow, right) phagocytosing anthrax bacilli (orange, left). (CC BY 2.5; Volker Brinkmann via PLOS).

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SECTION OVERVIEW

11.1: Overview of Immunity

Topic hierarchy

11.1A: Cells and Organs of the Immune System

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11.1C: Overview of the Immune System

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11.1A: Cells and Organs of the Immune System

The immune system includes primary lymphoid organs, secondary lymphatic tissues and various cells in the innate and adaptive immune systems.

Learning Objectives

- Recognize the cells and organs of the immune system and their functions

Key Points

- The key primary lymphoid organs of the immune system are the thymus and bone marrow, and secondary lymphatic tissues such as spleen, tonsils, lymph vessels, lymph nodes, adenoids, and skin and liver.
- Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system.
- The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens and are also important mediators in the activation of the adaptive immune system.
- The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow.
- The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels. The lymphatic system has multiple functions such as the transportation of white blood cells to and from the lymph nodes into the bones.

Key Terms

- **lymphocytes**: A lymphocyte is a type of white blood cell in the vertebrate immune system. The three major types of lymphocyte are T cells, B cells and natural killer (NK) cells. T cells (thymus cells) and B cells (bursa-derived cells) are the major cellular components of the adaptive immune response.
- **Leukocytes**: Cells of the immune system involved in defending the body against both infectious disease and foreign materials. Five different and diverse types of leukocytes exist.

Immune System Organs

The key primary lymphoid organs of the immune system include the thymus and bone marrow, as well as secondary lymphatic tissues including spleen, tonsils, lymph vessels, lymph nodes, adenoids, skin, and liver.

The thymus “educates” T cells and provides an inductive environment for the development of T cells from hematopoietic progenitor cells. The thymus is largest and most active during the neonatal and pre-adolescent periods of development. By the early teens, the thymus begins to atrophy and thymic stroma is replaced by adipose tissue. Nevertheless, residual T-lymphopoiesis continues throughout adult life.

Bone marrow is the flexible tissue found in the interior of bones. In humans, red blood cells are produced in the heads of long bones. The red bone marrow is a key element of the lymphatic system, being one of the primary lymphoid organs that generate lymphocytes from immature hematopoietic progenitor cells. Bone marrow and thymus constitute the primary lymphoid tissues involved in the production and early selection of lymphocytes.

The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels that carry a clear fluid, called lymph, unidirectionally towards the heart. The lymphatic system has multiple interrelated functions including the transportation of white blood cells to and from the lymph nodes into the bones, and the transportation of antigen -presenting cells (such as dendritic cells) to the lymph nodes where an immune response is stimulated. Lymphoid tissue is found in many organs, particularly the lymph nodes.

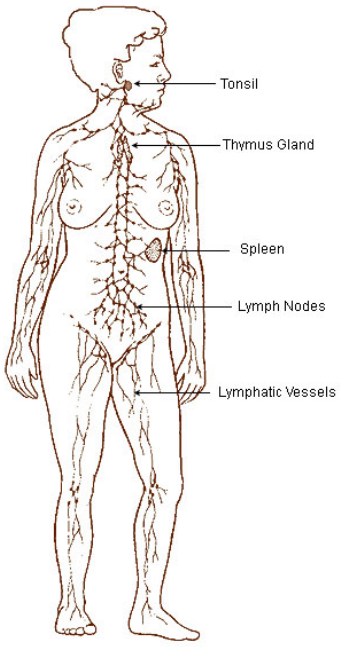

Figure: **The Lymph Nodes and Lymph Vessels in Human Beings**: The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels that carry a clear fluid called lymph.

The spleen is similar in structure to a large lymph node and acts primarily as a blood filter. It synthesizes antibodies in its white pulp and removes antibody-coated bacteria along with antibody-coated blood cells by way of blood and lymph node circulation.

The palatine tonsils and the nasopharyngeal tonsil are lymphoepithelial tissues located near the oropharynx and nasopharynx. These immunocompetent tissues are the immune system's first line of defense against ingested or inhaled foreign pathogens. The fundamental immunological roles of tonsils aren't yet understood.

Lymph nodes are distributed widely throughout areas of the body, including the armpit and stomach, and linked by lymphatic vessels. Lymph nodes are garrisons of B, T and other immune cells. Lymph nodes act as filters or traps for foreign particles and are important in the proper functioning of the immune system. They are packed tightly with the white blood cells, called lymphocytes and macrophages.

The skin is one of the most important parts of the body because it interfaces with the environment, and is the first line of defense from external factors, acting as an anatomical barrier from pathogens and damage between the internal and external environment in bodily defense. Langerhans cells in the skin are part of the adaptive immune system.

The liver has a wide range of functions, including immunological effects—the reticuloendothelial system of the liver contains many immunologically active cells, acting as a "sieve" for antigens carried to it via the portal system.

Immune System Cells

Leukocytes (white blood cells) are immune system cells involved in defending the body against infectious disease and foreign materials. Five different types of leukocytes exist, all produced and derived from a multipotent cell in the bone marrow known as a hematopoietic stem cell. The innate leukocytes include the phagocytes, mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens and are important mediators in the activation of the adaptive immune system.

Neutrophils and macrophages are phagocytes that travel throughout the body in pursuit of invading pathogens. Neutrophils are normally found in the bloodstream and are the most abundant type of phagocyte. During the acute phase of inflammation neutrophils migrate toward the site of inflammation and are usually the first cells to arrive at the scene of infection. Macrophages reside within tissues and produce a wide array of chemicals. They also act as scavengers, ridding the body of worn-out cells and other debris, and as antigen-presenting cells that activate the adaptive immune system. Dendritic cells are phagocytes in tissues that are in contact with the external environment, and are located mainly in the skin, nose, lungs, stomach, and intestines. These cells serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigen to T-cells, one of the key cell types of the adaptive immune system.

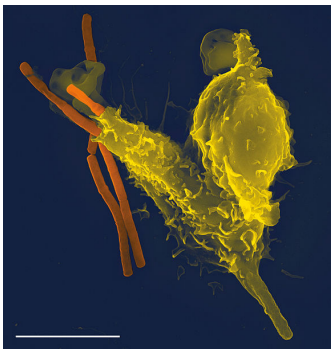

Figure: **A Phagocyte in Action**: Neutrophil engulfing anthrax bacteria. Taken with a Leo 1550 scanning electron microscope. Scale bar is 5 micrometers.

Mast cells reside in connective tissues and mucous membranes, and regulate the inflammatory response. They are most often associated with allergy and anaphylaxis.

Basophils and eosinophils are related to neutrophils. They secrete chemical mediators that are involved in defending against parasites, and play a role in allergic reactions, such as asthma.

Natural killer cells are leukocytes that attack and destroy tumor cells, or cells that have been infected by viruses.

The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow.

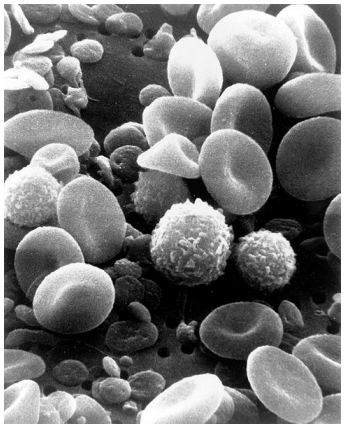

Figure: **Blood Cells**: Red blood cells, several white blood cells including lymphocytes, a monocyte, a neutrophil, and many small disc-shaped platelets.

T cells recognize a “non-self” target, such as a pathogen, only after antigens have been processed and presented in combination with a “self” receptor, called a major histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: the killer T cell, which kills cells that are infected with viruses (and other pathogens) or are otherwise damaged or dysfunctional, and the helper T cell, which regulates both innate and adaptive immune responses and helps determine which immune responses the body makes to a particular pathogen. These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. A third, minor subtype are the γ T cells that recognize intact antigens not bound to MHC receptors.

In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, which recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture.

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11.1B: Overview of Human-Microbial Reactions

Learning Objectives

- Outline the relationships between humans and microbes: non-pathogenic and pathogenic

The Human Microbiome Project

The Human Microbiome Project (HMP) is a United States National Institutes of Health initiative aimed at identifying and characterizing the microorganisms which are found in association with both healthy and diseased humans.

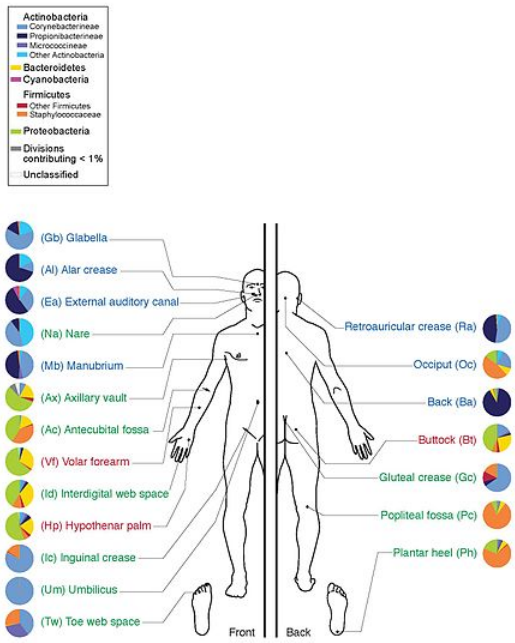

Figure: ***Bacteria commonly found in and on humans****: This is a depiction of the human body and bacteria that predominates throughout it.*

Total microbial cells found in association with humans may exceed the total number of cells making up the human body by a factor of ten-to-one. The total number of genes associated with the human microbiome could exceed the total number of human genes by a factor of 100-to-one.

Organisms expected to be found in the human microbiome may generally be categorized as bacteria (the majority), archaea, yeasts, and single-celled eukaryotes as well as various helminth parasites and viruses, such as those that infect cellular microbiome organisms.

The HMP project discovered several “surprises”, including:

- Bacterial protein -coding genes are estimated as 360 times more abundant than human genes.
- Microbial metabolic activities, for example, digestion of fats, are not always provided by the same bacterial species.
- Components of the human microbiome change over time, affected by a patient disease state and medication.

Examples of Non-pathogenic Interactions

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora. The human body, consisting of about 10 trillion cells, carries about ten times as many microorganisms in the intestines. The metabolic activities performed by these bacteria resemble those of an organ, leading some to liken gut bacteria to a “forgotten” organ.

Bacteria make up most of the flora in the colon and up to 60% of the dry mass of feces. Between 300 and 1000 different species live in the gut. It is probable that 99% of the bacteria come from about 30 or 40 species. Fungi and protozoa also make up a part of the gut flora, but little is known about their activities.

The relationship between gut flora and humans is thought to be not merely commensal, but rather a mutualistic relationship. Though people can survive without gut flora, the microorganisms perform a host of useful functions, such as fermenting unused energy substrates, training the immune system, preventing growth of harmful, pathogenic bacteria, regulating the development of the gut, producing vitamins for the host, and producing hormones to direct the host to store fats. In certain conditions, some species can cause disease by producing infection or increasing the host's cancer risk.

The skin microbiota are composed mostly of bacteria of which there are around 1000 species upon human skin from 19 phyla. The total number of bacteria on an average human has been estimated at 10^{12}.

Skin flora are usually non-pathogenic and either commensal or mutualistic. The benefits of bacteria include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system. Resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people.

Pathogenic Interactions

Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. Infectious diseases comprise clinically evident illness resulting from the infection, and the presence and growth of pathogenic biological agents in an individual host organism. Infectious pathogens include some viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions. Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host. Their intrinsic virulence is due to their need to reproduce and spread.

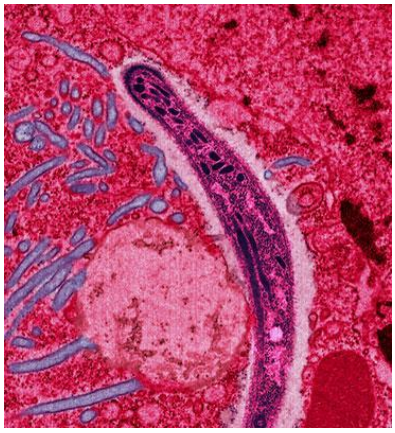

Figure: ***The malaria plasmodium****: Malaria is transmitted to people and animals by mosquitoes. Malarial sporozoites develop inside oocysts and are released in large numbers into the hemocoel of Anopheles stephensi mosquitoes. This false-colored electron micrograph shows a sporozoite migrating through the cytoplasm of midgut epithelia.*

Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens. Opportunistic disease may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal tract. They may also result from (otherwise innocuous) microbes acquired from other hosts or from the environment as a result of traumatic introduction (as in surgical wound infections). An opportunistic disease requires impairment of host defenses, which may occur as a result of genetic defects, exposure to antimicrobial drugs or immunosuppressive chemicals, exposure to ionizing radiation, or as a result of an infectious disease with immunosuppressive activity.

The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading the immune system. Bacteria often overcome physical barriers by secreting enzymes that digest the barrier. An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host. The mechanisms used to evade the adaptive immune system are more complicated. The simplest approach is antigenic variation: rapid changes of non-essential epitopes on the surface of the pathogen, while keeping essential epitopes concealed.

Key Points

- Though people can survive without gut flora, the microorganisms perform a host of useful functions: fermenting unused energy substrates, training the immune system, preventing growth of harmful bacteria, regulating the development of the gut, and

producing vitamins and hormones for the host.

- Organisms expected to be found in the human microbiome may generally be categorized as bacteria (the majority), archaea, yeasts, and single-celled eukaryotes as well as various helminth parasites and viruses.
- Skin flora are usually either commensal or mutualistic. The benefits of bacteria include preventing transient pathogenic organisms from colonizing the skin surface. Resident microbes can cause skin diseases and create life-threatening illness particularly in immunosuppressed people.
- Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect.
- Primary pathogens cause disease as a result of their activity in the healthy host and their intrinsic virulence is due to their need to reproduce and spread. Organisms that cause an infectious disease in a host with depressed resistance are classified as opportunistic.
- The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading the immune system.

Key Terms

- **Human microbiome**: The aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect.
- **Primary pathogen**: These pathogens cause disease as a result of their presence or activity within the normal, healthy host. Their intrinsic virulence (the severity of the disease they cause) is due to their need to reproduce and spread.
- **Opportunistic pathogen**: Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens. Opportunistic disease may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal or the upper respiratory tract. They may also result from (otherwise innocuous) microbes acquired from other hosts or from the environment as a result of traumatic introduction. An opportunistic disease requires impairment of host defenses.

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11.1C: Overview of the Immune System

The immune system is a system of biological structures and processes within an organism that protects against disease.

Learning Objectives

- Distinguish between innate and adaptive immunity

Key Points

- Pathogens can rapidly evolve and adapt to avoid detection and neutralization by the immune system. As a result, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. The immune system protects from infection with layered defenses of increasing specificity.
- Physical barriers prevent pathogens from entering the organism. If these barriers are breached, the innate immune system provides an immediate, non-specific response. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system.
- Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion.
- Innate, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches.
- Adaptive immunity is often sub-divided into two major types acording to how the immunity was introduced. Naturally acquired immunity occurs through non-deliberate contact with a disease causing agent, whereas artificially acquired immunity develops through deliberate actions such as vaccination.
- Immunology is a branch of biomedical science that covers the study of all aspects of the immune system in all organisms. It deals with the physiological functioning of the immune system in states of both health and disease.

Key Terms

- **Adaptive (acquired) immunity**: The creation of immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.
- **Innate immunity**: The natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches.
- **Self molecules**: Those components of an organism's body that can be distinguished by the immune system from foreign substances.

The immune system is a system of biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue.

Pathogens can rapidly evolve and adapt to avoid detection and neutralization by the immune system. As a result, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. Even simple unicellular organisms, such as bacteria, possess a rudimentary immune system in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms including include phagocytosis, antimicrobial peptides called defensins, and the complement system, which evolved in ancient eukaryotes and remain in modern descendants, such as plants and insects. Jawed vertebrates have even more sophisticated defense mechanisms, including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive (acquired) immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

Innate and Adaptive Immunity

The immune system protects organisms from infection with layered defenses of increasing specificity. Physical barriers prevent pathogens, such as bacteria and viruses, from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system, which is activated by the innate response. The immune system adapts its response during an infection in order to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological

memory, and allows the adaptive immune system to mount faster and stronger attacks when this pathogen is encountered. Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non- self molecules, where self molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system.

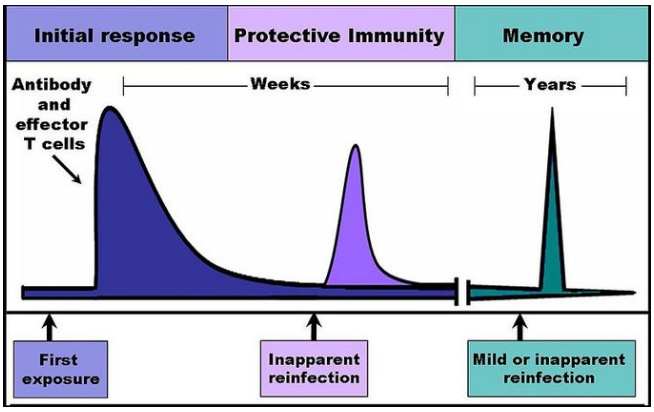

Figure: **The Time Course of an Immune Response**: Immune reactants, such as antibodies and effector T-cells, work to eliminate an infection, and their levels and activity rapidly increase following an encounter with an infectious agent, whether that agent is a pathogen or a vaccine. For several weeks these reactants remain in the serum and lymphatic tissues and provide protective immunity against reinfection by the same agent. During an early reinfection, few outward symptoms of illness are present, but the levels of immune reactants increase and are detectable in the blood and/or lymph. Following clearance of the infection, antibody level and effector T cell activity gradually declines. Because immunological memory has developed, reinfection at later times leads to a rapid increase in antibody production and effector T cell activity. These later infections can be mild or even inapparent.

Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion. Immunity involves both specific and non-specific components.

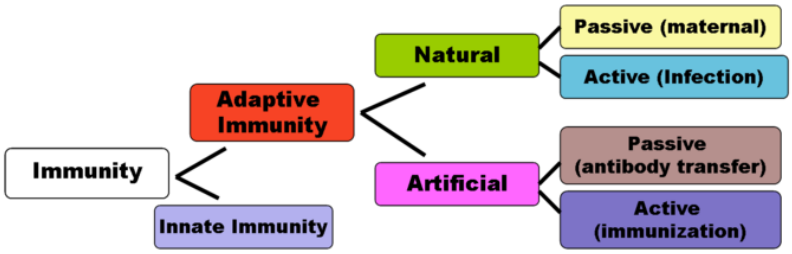

Figure: **Immunity**: Natural immunity occurs through contact with a disease causing agent, when the contact was not deliberate, where as artificial immunity develops only through deliberate actions of exposure. Both natural and artificial immunity can be further subdivided, depending on the amount of time the protection lasts. Passive immunity is short lived, and usually lasts only a few months, whereas protection via active immunity lasts much longer, and is sometimes life-long.

INNATE IMMUNITY

Innate, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches. Microbes first encounter the epithelial layers (physical barriers that line our skin and mucous membranes). Subsequent general defenses include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory response. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these approaches, innate immunity can prevent the colonization, entry, and spread of microbes.

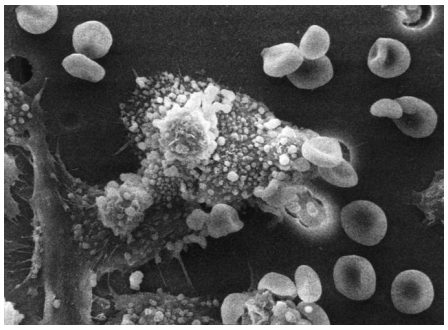

Figure: **An animal's immune response to a foreign body**: Macrophages begin to fuse with, and inject its toxins into, the cancer cell. The cell starts rounding up and loses its spikes. As the macrophage cell becomes smooth. The cancer cell appears lumpy in the last stage before it dies. These lumps are actually the macrophages fused within the cancer cell. The cancer cell then loses its morphology, shrinks up and dies. Photo magnification: 3: x8,000 Type: B & W print

ADAPTIVE IMMUNITY

Adaptive immunity is often sub-divided into two major types depending on how the immunity was introduced. Naturally acquired immunity occurs through contact with a disease causing agent, when the contact was not deliberate, whereas artificially acquired immunity develops only through deliberate actions such as vaccination. Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from an immune host. Passive immunity is acquired through transfer of antibodies or activated T cells from an immune host, and is short lived—usually lasting only a few months. Active immunity is induced in the host itself by antigen, and lasts much longer, sometimes the entire lifetime.

A further subdivision of adaptive immunity is characterized by the cells involved; humoral immunity is the aspect of immunity that is mediated by secreted antibodies, whereas the protection provided by cell-mediated immunity involves T lymphocytes alone. Humoral immunity is active when the organism generates its own antibodies, and passive when antibodies are transferred between individuals. Similarly, cell-mediated immunity is active when the organism's own T cells are stimulated and passive when T cells come from another organism.

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SECTION OVERVIEW

11.2: The Innate Immune Response

Topic hierarchy

11.3A: Natural Killer Cells

11.3B: Physical and Chemical Barriers

11.3C: The Complement System

11.3D: Pathogen Recognition

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11.3A: Natural Killer Cells

LEARNING OBJECTIVe

- Describe the role of natural killer cells in the immune response

Lymphocytes are leukocytes (white blood cells) that are histologically identifiable by their large, darkly-staining nuclei; they are small cells with very little cytoplasm. After a pathogen enters the body, infected cells are identified and destroyed by natural killer (NK) cells, which are a type of lymphocyte that can kill cells infected with viruses or tumor cells (abnormal cells that uncontrollably divide and invade other tissue). While NK cells are part of the innate immune response, they are best understood relative to their counterparts in the adaptive immune response,T cells, which are also classified as lymphocytes.

T cells are lymphocytes that mature in the thymus gland and identify intracellular infections, especially from viruses, by the altered expression of major histocompatibility class (MHC) I molecules on the surface of infected cells. MHC I molecules are proteins on the surfaces of all nucleated cells which help the immune system distinguish between “self” and “non-self.” If the cell is infected, the MHC I molecules display fragments of proteins from the infectious agents to T-cells. Healthy cells do not display any proteins and will be ignored by the immune system, while the cells identified as “non-self” by foreign proteins will be attacked by the immune system.

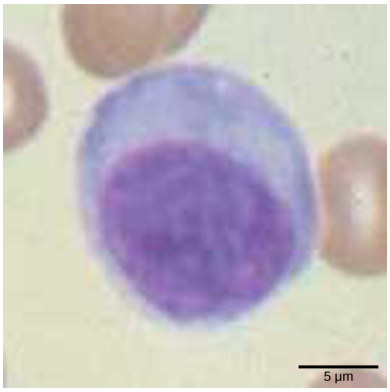

Figure: ***Lymphocytes****: Lymphocytes, such as NK cells, are characterized by their large nuclei that actively absorb Wright stain and, therefore, appear dark colored under a microscope.*

An infected cell (or a tumor cell) is often incapable of synthesizing and displaying MHC I molecules appropriately. The metabolic resources of cells infected by some viruses produce proteins that interfere with MHC I processing and/or trafficking to the cell surface. The reduced MHC I on host cells varies from virus to virus and results from active inhibitors being produced by the viruses. This process can deplete host MHC I molecules on the cell surface, which prevents T-cells from recognizing them, but which NK cells detect as “unhealthy” or “abnormal” while searching for cellular MHC I molecules. As such, NK cells offer a complementary check for unhealthy cells, relative to T cells. Similarly, the dramatically-altered gene expression of tumor cells leads to expression of extremely- deformed or absent MHC I molecules that also signal “unhealthy” or “abnormal.”

NK cells are always active; an interaction with normal, intact MHC I molecules on a healthy cell disables the killing sequence, causing the NK cell to move on. After the NK cell detects an infected or tumor cell, its cytoplasm secretes granules comprised of perforin: a destructive protein that creates a pore in the target cell. Granzymes are released along with the perforin in the immunological synapse. A granzyme, a protease that digests cellular proteins, induces the target cell to undergo programmed cell death, or apoptosis. Phagocytic cells then digest the cell debris left behind. NK cells are constantly patrolling the body. They are an effective mechanism for controlling potential infections and preventing cancer progression.

Key Points

- Natural killer (NK) cells are lymphocytes (a subclass of white blood cells) that recognize infected or tumorogenic cells and kill them.
- Unlike the related T cells, NK cells do not recognize fragments of the infecting particle, but rather the incorrect display of major histocompatibility complex (MHC) I molecules.
- NK cells are always active, but will not perform their killing function on cells with intact MHC I molecules.

- When NK cells detect an infected or tumor cell, they secrete granules that contain perforin, creating a pore in the target cell; granzymes then pass through these pores, degrading cellular proteins, causing cells to undergo apoptosis.

Key Terms

- **lymphocyte**: a type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-cells, T-cells, and natural killer (NK) cells
- **major histocompatibility complex**: a protein present on the extracellular surface of the cell that displays portions of the proteins that are degraded inside the cell
- **T cell**: a lymphocyte, from the thymus, that can recognize specific antigens and can activate or deactivate other immune cells

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11.3B: Physical and Chemical Barriers

The innate immune response has physical and chemical barriers that exist as the first line of defense against infectious pathogens.

Learning Objectives

- Describe physical and chemical barriers in the innate immune response

Key Points

- The skin, or epithelial surface, serves as the primary barrier to microbial entry into the body; skin peeling, drying out, and the skin's acidity all serve to dislodge or kill foreign pathogens.
- Orifices such as the eyes and mouth, which are not covered by skin, have other mechanisms by which they prevent entry; tears wash away microbes, while cilia in the nasal passages and respiratory tract push mucus (which traps pathogens) out of the body.
- Many chemical barriers also exist once pathogens make it past the outer physical barriers; the acidity of the stomach ensures that few organisms arriving with food survive the digestive system.

Key Terms

- **cilium**: a hairlike organelle projecting from a eukaryotic cell (such as unicellular organism or one cell of a multicelled organism), which serves either for locomotion by moving or as sensors
- **microbicidal**: functioning to reduce the infectivity of microbes

Physical and chemical barriers

The immune system comprises both innate and adaptive immune responses. Innate immunity occurs naturally due to genetic factors or physiology. It is not induced by infection or vaccination, but is constantly available to reduce the workload for the adaptive immune response. The adaptive immune response expands over time, storing information about past infections and mounting pathogen-specific defenses. Both the innate and adaptive levels of the immune response involve secreted proteins, receptor-mediated signaling, and intricate cell -to-cell communication. From an historical perspective, the innate immune system developed early in animal evolution, roughly a billion years ago, as an essential response to infection. In the innate immune response, any pathogenic threat triggers a consistent sequence of events that can identify the type of pathogen and either clear the infection independently or mobilize a highly-specialized adaptive immune response.

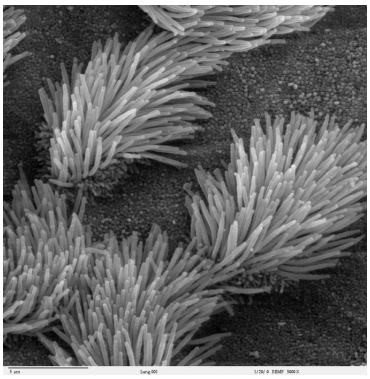

Figure: **Cilia up close**: Cilia are a type of organelle found in eukaryotic cells. In the innate immune system, they serve to move pathogens out of the respiratory system via a concerted sweeping motion.

Before any immune factors are triggered, the skin (also known as the epithelial surface) functions as a continuous, impassable barrier to potentially-infectious pathogens. The skin is considered the first defense of the innate immune system; it is the first of the nonspecific barrier defenses. Pathogens are killed or inactivated on the skin by desiccation (drying out) and by the skin's acidity. In addition, beneficial microorganisms that coexist on the skin compete with invading pathogens, preventing infection. Desquamation, or peeling skin, also serves to dislodge organisms that have adhered to the surface of the body and are awaiting entry. Regions of the body that are not protected by skin (such as the eyes and mucous membranes) have alternative methods of defense. These include tears in the eyes; mucous membranes that provide partial protection despite having to allow absorption and secretion; mucus secretions that trap and rinse away pathogens; and cilia (singular cilium) in the nasal passages and respiratory tract that push

the mucus with the pathogens out of the body. Furthermore, tears and mucus secretions contain microbicidal factors that prevent many infections from entering via these routes.

Despite these barriers, pathogens may enter the body through skin abrasions or punctures, or by collecting on mucosal surfaces in large numbers that overcome the mucus or cilia. Some pathogens have evolved specific mechanisms that allow them to overcome physical and chemical barriers.

Once inside, the body still has many other defenses, including chemical barriers. Some of these include the low pH of the stomach, which inhibits the growth of pathogens; blood proteins that bind and disrupt bacterial cell membranes; and the process of urination, which flushes pathogens from the urinary tract. The blood-brain barrier also protects the nervous system from pathogens that have already entered the blood stream, but would do significantly more damage if they entered the central nervous system.

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11.3C: The Complement System

Around 20 soluble proteins comprise the complement system, which helps destroy extracellular microorganisms that have invaded the body.

Learning Objectives

- Explain how the complement system aids antibody response

Key Points

- The complement system is so named because it is complementary to the antibody response of the adaptive immune system.
- The complement system proteins are produced continuously by the liver and macrophages, are abundant in the blood serum, and are capable of immediate response to infecting microorganisms.
- The complement system works by first having several proteins bind to a target; this binding event then begins a series of highly-specific and regulated sequences wherein successive proteins are activated by cleavage and/or structural changes of the preceding proteins.
- The complement system serves as a marker to indicate targets for phagocytic cells; complement proteins can also combine to form attack complexes capable of opening pores in microbial cell membranes.

Key Terms

- **opsonization**: the process by which a pathogen is marked for ingestion and destruction by a phagocyte
- **complement system**: an aspect of the innate immune system that supplements the actions of the antibodies and phagocytic cells in clearing out pathogens from an organism

Complement

The innate immune system serves as a first responder to pathogenic threats that bypass natural physical and chemical barriers of the body. Using a combination of cellular and molecular attacks, the innate immune system identifies the nature of a pathogen and responds with inflammation, phagocytosis (where a cell engulfs a foreign particle), cytokine release, destruction by NK cells, and/or a complement system. In this concept, we will discuss the complement system.

An array of approximately 20 types of soluble proteins, called a complement system, functions to destroy extracellular pathogens. Cells of the liver and macrophages synthesize complement proteins continuously. These proteins are abundant in the blood serum and are capable of responding immediately to infecting microorganisms. The complement system is so named because it is complementary to the antibody response of the adaptive immune system. Complement proteins bind to the surfaces of microorganisms and are particularly attracted to pathogens that are already bound by antibodies. Binding of complement proteins occurs in a specific and highly-regulated sequence, with each successive protein being activated by cleavage and/or structural changes induced upon binding of the preceding protein(s). After the first few complement proteins bind, a cascade of sequential binding events follows in which the pathogen rapidly becomes coated in complement proteins.

Complement proteins perform several functions. They serve as a marker to indicate the presence of a pathogen to phagocytic cells, such as macrophages and B cells, to enhance engulfment. This process is called opsonization. Certain complement proteins can combine to form attack complexes that open pores in microbial cell membranes. These structures destroy pathogens by causing their contents to leak. When innate mechanisms are insufficient to clear an infection, the adaptive immune response is informed and mobilized.

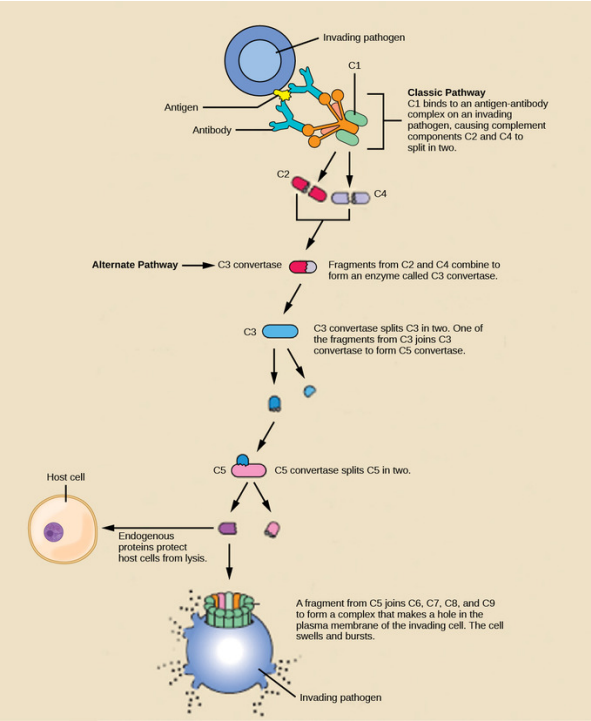

Figure: **Complement cascade in the innate immune response**: The classic pathway for the complement cascade involves the attachment of several initial complement proteins to an antibody-bound pathogen, followed by rapid activation and binding of many more complement proteins and the creation of destructive pores in the microbial cell envelope and cell wall. The alternate pathway does not involve antibody activation. Rather, C3 convertase spontaneously breaks down C3. Endogenous regulatory proteins prevent the complement complex from binding to host cells. Pathogens lacking these regulatory proteins are lysed.

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11.3D: Pathogen Recognition

Upon pathogen entry to the body, the innate immune system uses several mechanisms to destroy the pathogen and any cells it has infected.

Learning Objectives

- Describe the role of PAMPs and PRRs, interferons, and other cytokines in innate immunity

Key Points

- Pathogens are recognized by a variety of immune cells, such as macrophages and dendritic cells, via pathogen-associated molecular patterns (PAMPs) on the pathogen surface, which interact with complementary pattern-recognition receptors (PRRs) on the immune cells' surfaces.
- Upon binding of PRRs with PAMPs (pathogen recognition), immune cells release cytokines to tell other cells to start fighting back.
- One class of cytokines, interferons, warn nearby uninfected cells of impending infection, cause cells to start cleaving RNA and reduce protein synthesis, and signal nearby infected cells to undergo apoptosis.
- Another class of cytokines, called inerleukins, mediate interactions between white blood cells (leukocytes) and help bridge the innate and adaptive immune responses.
- Inflammation (hot, red, swollen, painful tissue associated with infection) is encouraged by cytokines that are produced immediately upon pathogen recognition; the increase in blood flow associated with inflammation allows more leukocytes (a type of innate immune cell) to reach the infected area.

Key Terms

- **macrophage**: a white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink; part of the innate immune system
- **phagocytosis**: the process where a cell incorporates a particle by extending pseudopodia and drawing the particle into a vacuole of its cytoplasm
- **cytokine**: any of various small regulatory proteins that regulate the cells of the immune system; they are released upon binding of PRRs to PAMPS

Pathogen recognition

When a pathogen enters the body, cells in the blood and lymph detect the specific pathogen-associated molecular patterns (PAMPs) on the pathogen's surface. PAMPs are carbohydrate, polypeptide, and nucleic acid "signatures" that are expressed by viruses, bacteria, and parasites, but which differ from molecules on host cells. These PAMPs allow the immune system to recognize "self" from "other" so as not to destroy the host.

The immune system has specific cells with receptors that recognize these PAMPs. A macrophage is a large, phagocytic cell that engulfs foreign particles and pathogens. Macrophages recognize PAMPs via complementary pattern recognition receptors (PRRs). PRRs are molecules on macrophages and dendritic cells which are in contact with the external environment and can thus recognize PAMPs when present. A monocyte, a type of leukocyte (white blood cell) that circulates in the blood and lymph, differentiates into macrophages after it moves into infected tissue. Dendritic cells bind molecular signatures of pathogens, promoting pathogen engulfment and destruction.

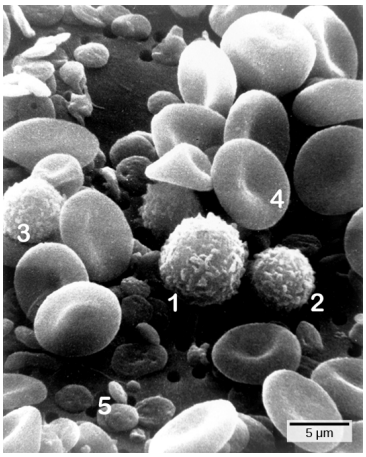

Figure: **Blood cells related to the innate immune response**: Cells of the blood include (1) monocytes, (2) lymphocytes, (3) neutrophils, (4) red blood cells, and (5) platelets. Leukocytes (1, 2, 3) are white blood cells that play an important role in the body's immune system.

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

Figure: **Cells involved in the innate immune system**: The immune system has specific cells whose job is to recognize pathogen-associated molecular patterns. The characteristics and location of cells involved in the innate immune system are described in this chart.

Once a pathogen is detected, the immune system must also track whether it is replicating intracellularly (inside the cell, as with most viruses and some bacteria) or extracellularly (outside of the cell, as with other bacteria, but not viruses). The innate immune system must respond accordingly by identifying the extracellular pathogen and/or by identifying host cells that have already been infected.

Cytokine release affect

The binding of PRRs with PAMPs triggers the release of cytokines, which signal that a pathogen is present and needs to be destroyed along with any infected cells. A cytokine is a chemical messenger that regulates cell differentiation (form and function), proliferation (production), and gene expression to affect immune responses. At least 40 types of cytokines exist in humans that differ in terms of the cell type that produces them, the cell type that responds to them, and the changes they produce.

One subclass of cytokines is the interleukin (IL), which mediates interactions between leukocytes (white blood cells). Interleukins are involved in bridging the innate and adaptive immune responses. In addition to being released from cells after PAMP recognition, cytokines are released by the infected cells which bind to nearby uninfected cells, inducing those cells to release cytokines, resulting in a cytokine burst.

A second class of cytokines is interferons, which are released by infected cells as a warning to nearby uninfected cells. A function an interferons is to inhibit viral replication, making them particularly effective against viruses. They also have other important functions, such as tumor surveillance. Interferons work by signaling neighboring uninfected cells to destroy RNA (often a very important biomolecule for viruses) and reduce protein synthesis; signaling neighboring infected cells to undergo apoptosis (programmed cell death); and activating immune cells.

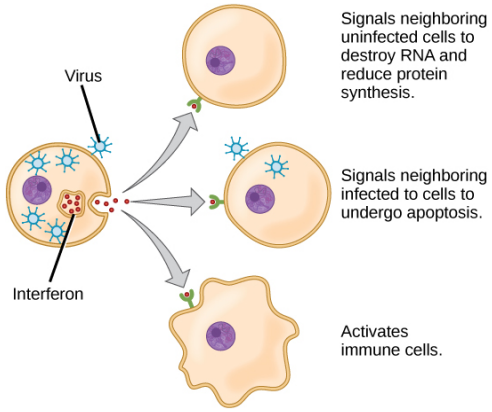

Figure: **Interferon release**: Interferons are cytokines that are released by a cell infected with a virus. The response of neighboring cells to interferons helps stem the infection.

Cytokines also send feedback to cells of the nervous system to bring about the overall symptoms of feeling sick, which include lethargy, muscle pain, and nausea. These effects may have evolved because the symptoms encourage the individual to rest, preventing them from spreading the infection to others. Cytokines also increase the core body temperature, causing a fever, which causes the liver to withhold iron from the blood. Without iron, certain pathogens (such as some bacteria) are unable to replicate; this is called nutritional immunity.

Phagocytosis and inflammation

The first cytokines to be produced are pro-inflammatory; that is, they encourage inflammation, or the localized redness, swelling (edema), heat, loss of function, and pain that result from the movement of leukocytes and fluid through increasingly-permeable capillaries to a site of infection. The population of leukocytes that arrives at an infection site depends on the nature of the infecting pathogen. Both macrophages and dendritic cells engulf pathogens and cellular debris through phagocytosis. A neutrophil is also a phagocytic leukocyte that engulfs and digests pathogens. Neutrophils, the most-abundant leukocytes of the immune system, have a nucleus with two to five lobes and contain organelles (lysosomes) that digest engulfed pathogens. An eosinophil is a leukocyte that works with other eosinophils to surround a parasite. It is involved in the allergic response and in protection against helminthes (parasitic worms).

Neutrophils and eosinophils are particularly important leukocytes that engulf large pathogens, such as bacteria and fungi. A mast cell is a leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens. A basophil is a leukocyte that, like a neutrophil, releases chemicals to stimulate the inflammatory response. Basophils are also involved in allergy and hypersensitivity responses and induce specific types of inflammatory responses. Eosinophils and basophils produce additional inflammatory mediators to recruit more leukocytes. A hypersensitive immune response to harmless antigens, such as in pollen, often involves the release of histamine by basophils and mast cells; this is why many anti-allergy medications are anti-histamines.

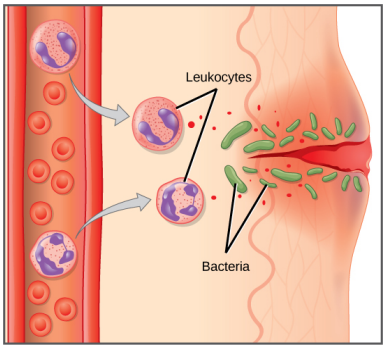

Figure: **Innate immune response to cuts**: In response to a cut, mast cells secrete histamines that cause nearby capillaries to dilate. Neutrophils and monocytes leave the capillaries. Monocytes mature into macrophages. Neutrophils, dendritic cells, and macrophages release chemicals to stimulate the inflammatory response. Neutrophils and macrophages also consume invading bacteria by phagocytosis.

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SECTION OVERVIEW

11.3: Phagocytes

Topic hierarchy

11.4A: Phagocyte Migration and Phagocytosis

11.4B: Antigen-presenting Cells - B and T cells

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11.4A: Phagocyte Migration and Phagocytosis

Learning Objectives

- Summarize phagocytosis and phagocyte migration

Phagocytosis is the process by which a cell takes in particles such as bacteria, parasites, dead host cells, and cellular and foreign debris. It involves a chain of molecular processes. Phagocytosis occurs after the foreign body, a bacterial cell, for example, has bound to molecules called “receptors” that are on the surface of the phagocyte. The phagocyte then stretches itself around the bacterium and engulfs it. *Phagocytosis* of bacteria by human neutrophils takes on average nine minutes to occur. Once inside the phagocyte, the bacterium is trapped in a compartment called a phagosome. Within one minute the phagosome merges with either a lysosome or a granule, to form a phagolysosome. The bacterium is then subjected to an overwhelming array of killing mechanisms and is dead a few minutes later. Dendritic cells and macrophages, on the other hand, are not so fast, and phagocytosis can take many hours in these cells. Macrophages are slow and untidy eaters; they engulf huge quantities of material and frequently release some undigested material back into the tissues. This debris serves as a signal to recruit more phagocytes from the blood. Phagocytes have voracious appetites; scientists have even fed macrophages with iron filings and then used a small magnet to separate them from other cells.

All phagocytes, and especially macrophages, exist in degrees of readiness. Macrophages are usually relatively dormant in the tissues and proliferate slowly. In this semi-resting state, they clear away dead host cells and other non-infectious debris and rarely take part in antigen presentation. But, during an infection, they receive chemical signals—usually interferon gamma—which increases their production of MHC II molecules and which prepares them for presenting antigens. In this state, macrophages are good antigen presenters and killers. However, if they receive a signal directly from an invader, they become “hyperactivated”, stop proliferating, and concentrate on killing. Their size and rate of phagocytosis increases—some become large enough to engulf invading protozoa. In the blood, neutrophils are inactive but are swept along at high speed. When they receive signals from macrophages at the sites of inflammation, they slow down and leave the blood. In the tissues, they are activated by cytokines and arrive at the battle scene ready to kill.

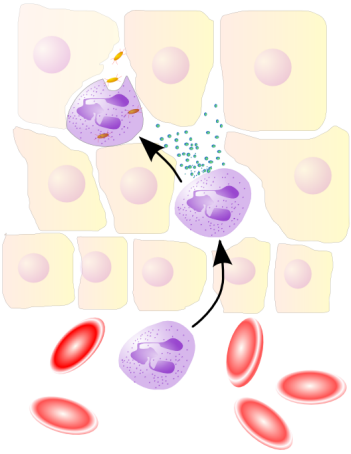

Figure: **Neutrophils**: Neutrophils move through the blood to the site of infection.

When an infection occurs, a chemical “SOS” signal is given off to attract phagocytes to the site. These chemical signals may include proteins from invading bacteria, clotting system peptides, complement products, and cytokines that have been given off by macrophages located in the tissue near the infection site. Another group of chemical attractants are cytokines that recruit neutrophils and monocytes from the blood. To reach the site of infection, phagocytes leave the bloodstream and enter the affected tissues. Signals from the infection cause the endothelial cells that line the blood vessels to make a protein called selectin, which neutrophils stick to when they pass by. Other signals called vasodilators loosen the junctions connecting endothelial cells, allowing the phagocytes to pass through the wall. Chemotaxis is the process by which phagocytes follow the cytokine “scent” to the infected spot. Neutrophils travel across epithelial cell-lined organs to sites of infection, and although this is an important component of fighting infection, the migration itself can result in disease-like symptoms. During an infection, millions of neutrophils are recruited from the blood, but they die after a few days.

Key Points

- Phagocytosis is needed to clear many things from a body, especially during an infection, when specialized cells “eat” things such as cellular debris or invading microbes.
- There are different cells that can engulf or phagocytose material in the body, these include macrophages, dendritic cells, and neutrophils.
- Phagocytic cells can migrate to a location where they are needed, through signaling events in the body.

Key Terms

- **neutrophil**: Neutrophil granulocytes are the most abundant type of white blood cells in mammals and form an essential part of the innate immune system.
- **metachromatic granule**: a granular cell inclusion present in many bacterial cells, having an avidity for basic dyes and causing irregular staining of the cell
- **macrophage**: A white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink. It presents foreign antigens on MHC II to lymphocytes. Part of the innate immune system.

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11.4B: Antigen-presenting Cells - B and T cells

Learning Objectives

- Explain the role played by B and T cells in the adaptive immune system

The adaptive, or acquired, immune response to an initial infection takes days or even weeks to become established, much longer than the innate response. However, adaptive immunity is more specific to an invading pathogen and can fight back much more quickly than the innate response if it has seen the pathogen before. Adaptive immunity occurs after exposure to an antigen either from a pathogen or a vaccination. An antigen is a molecule that binds to a specific antibody, often stimulating a response in the immune system as a result.

The adaptive immune response activates when the innate immune response insufficiently controls an infection. In fact, without information from the innate immune system, the adaptive response could not be mobilized. There are two types of adaptive responses: the cell-mediated immune response, which is controlled by activated T cells, and the humoral immune response, which is controlled by activated B cells and antibodies. Upon infection, activated T and B cells that have surface binding sites with specificity to the molecules on the pathogen greatly increase in number and attack the invading pathogen. Their attack can kill pathogens directly or they can secrete antibodies that enhance the phagocytosis of pathogens and disrupt the infection. Adaptive immunity also involves a memory, which gives the host long-term protection from reinfection by the same type of pathogen; upon re-exposure, this host memory will facilitate a rapid and powerful response.

B and T Cells

Lymphocytes, which are white blood cells, are formed with other blood cells in the red bone marrow found in many flat bones, such as the shoulder or pelvic bones. The two types of lymphocytes of the adaptive immune response are B and T cells. Whether an immature lymphocyte becomes a B cell or T cell depends on where in the body it matures. The B cells remain in the bone marrow to mature (hence the name “B” for “bone marrow”), while T cells migrate to the thymus, where they mature (hence the name “T” for “thymus”).

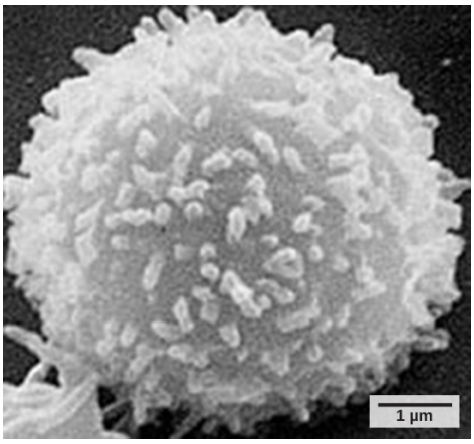

Figure: ***T cell by SEM****: This scanning electron micrograph shows a T lymphocyte. T and B cells are indistinguishable by light microscopy, but can be differentiated experimentally by probing their surface receptors.*

B Cell Receptors

The maturation of a B or T cell involves becoming immunocompetent, meaning that it can recognize and bind to a specific molecule or antigen. This recognition, which is central to the functioning of the adaptive immune response, results from the presence of highly specific receptors on the surfaces of B and T cells. On B cells, these receptors contain antibodies, which are responsible for antigen binding. An antibody is specific for one particular antigen; typically, it will not bind to anything else. Upon antigen binding to a B cell receptor, a signal is sent into the B cell to turn on an immune response.

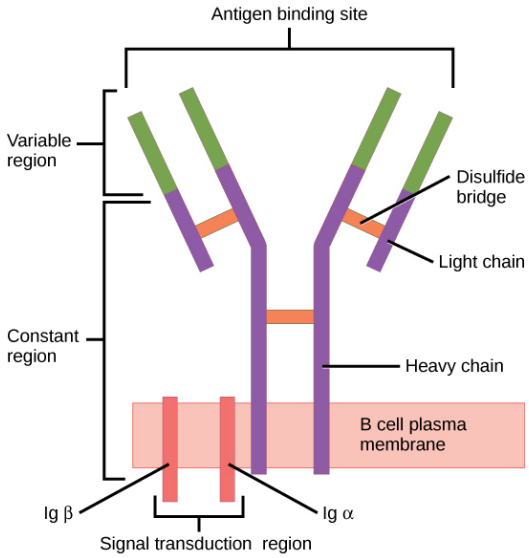

Figure: ***B cell receptors****: B cell receptors are embedded in the membranes of B cells and bind a variety of antigens through their variable regions, or antibodies. The signal transduction region transfers the signal into the cell.*

T Cell Receptors

Meanwhile, T cell receptors are responsible for the recognition of pathogenic antigens by T cells. Unlike B cells, T cells do not directly recognize antigens. Instead, they recognize antigens presented on major histocompatibility complexes (MHCs) that cells use to display which proteins are inside of them. If a cell is infected, it will present antigenic portions of the infecting pathogen on its MHC for recognition by T cells, which will then mount an appropriate immune response. Unlike antibodies, which can typically bind one and only one antigen, T cell receptors have more flexibility in their capacity to recognize antigens presented by MHCs.

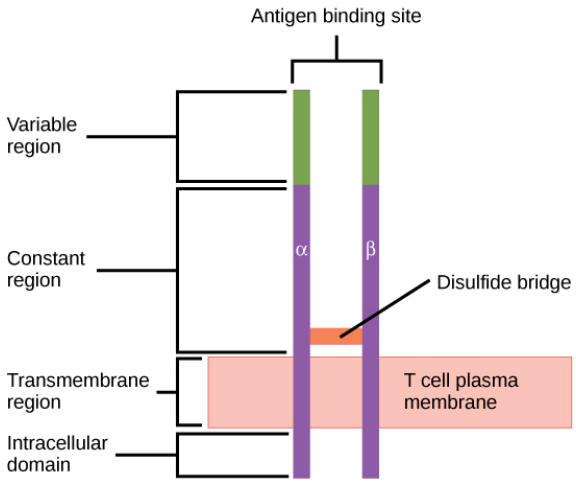

Figure: ***T cell receptors (TCRs)****: A T cell receptor spans the membrane and projects variable binding regions into the extracellular space to bind processed antigens via MHC molecules on APCs.*

It is the specific pathogen recognition (via binding antigens) of B and T cells that allows the adaptive immune response to adapt. During the maturation process, B and T cells that bind too strongly to the body's own cells' antigens are eliminated in order to minimize an immune response against the body's own tissues. Only those cells that react weakly to the body's own cells will remain. This process occurs during fetal development and continues throughout life. Once they are immunocompetent, the T and B cells migrate to the spleen and lymph nodes where they remain until they are called on during an infection. B cells are involved in the humoral immune response, which targets pathogens loose in blood and lymph, while T cells are involved in the cell-mediated immune response, which targets infected cells.

Key Points

- The adaptive immune response is slower to develop than the innate immune response, but it can act much more powerfully and quickly than the innate immune response against pathogens that it has seen before.
- B and T cells are lymphocytes, or white blood cells, which are able to recognize antigens that distinguish “self” from “other” in the body.
- B and T cells that recognize “self” antigens are destroyed before they can mature; this helps to prevent the immune system from attacking its own body.

Key Terms

- **B cell**: a lymphocyte, developed in the bursa of birds and the bone marrow of other animals, that produces antibodies and is responsible for the immune system
- **T cell**: a lymphocyte, from the thymus, that can recognize specific antigens and can activate or deactivate other immune cells
- **antigen**: a substance that binds to a specific antibody; may cause an immune response

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SECTION OVERVIEW

11.4: Innate Defenders

Topic hierarchy

11.4A: The Complement System

11.4B: Interferons

11.4C: Natural Killer Cells

11.4D: Toll-Like Receptors

11.4E: Iron-Binding Proteins

11.4F: Antimicrobial Peptides

11.4G: The Complement System and Heart Disease

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11.4A: The Complement System

The complement system helps or “complements” the ability of antibodies and phagocytic cells to clear pathogens from an organism.

Learning Objectives

- Illustrate the key points of the complement system

Key Points

- Three biochemical pathways activate the complement system–the classical complement pathway, the alternative complement pathway, and the lectin pathway.
- The following are the basic functions of the complement: Opsonization (enhancing phagocytosis of antigens); chemotaxis (attracting macrophages and neutrophils); cell lysis (rupturing membranes of foreign cells); and clumping (antigen-bearing agents).
- The complement system consists of a number of small proteins found in the blood, generally synthesized by the liver, and normally circulating as inactive precursors (pro-proteins).

Key Terms

- **antibodies**: An antibody (Ab), also known as an immunoglobulin (Ig), is a large Y-shaped protein produced by B-cells that is used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses. The antibody recognizes a unique part of the foreign target, called an “antigen. “
- **phagocytic**: Phagocytosis, meaning “cell,” and -osis, meaning “process,” is the cellular process of engulfing solid particles by the cell membrane to form an internal phagosome by phagocytes and protists.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.
- **classical pathway**: a group of blood proteins that mediate the specific antibody response

The complement system helps or “complements” the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the immune system called the ” innate immune system ” that is not adaptable and does not change over the course of an individual’s lifetime. However, it can be recruited and brought into action by the adaptive immune system.

The complement system consists of a number of small proteins found in the blood, generally synthesized by the liver, and normally circulating as inactive precursors (pro-proteins). When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages. The end result of this activation cascade is massive amplification of the response and activation of the cell-killing membrane attack complex. Over 25 proteins and protein fragments make up the complement system, including serum proteins, serosal proteins, and cell membrane receptors. They account for about 5% of the globulin fraction of blood serum.

Three biochemical pathways activate the complement system: the classical complement pathway, the alternative complement pathway, and the lectin pathway. The following are the basic functions of the complement: opsonization (enhancing phagocytosis of antigens); chemotaxis (attracting macrophages and neutrophils); cell lysis (rupturing membranes of foreign cells); and clumping (antigen-bearing agents).

The proteins and glycoproteins that constitute the complement system are synthesized by the liver hepatocytes. But significant amounts are also produced by tissue macrophages, blood monocytes, and epithelial cells of the genitourinal tract and gastrointestinal tract. The three pathways of activation all generate homologous variants of the protease C3-convertase. The classical complement pathway typically requires antigen, antibody complexes for activation (specific immune response), whereas the alternative and mannose-binding lectin pathways can be activated by C3 hydrolysis or antigens without the presence of antibodies (non-specific immune response). In all three pathways, C3-convertase cleaves and activates component C3, creating C3a and C3b, and causing a cascade of further cleavage and activation events. C3b binds to the surface of pathogens, leading to greater internalization by phagocytic cells by opsonization. C5a is an important chemotactic protein, helping recruit inflammatory cells.

C3a is the precursor of an important cytokine (adipokine) named ASP and is usually rapidly cleaved by carboxypeptidase B. Both C3a and C5a have anaphylatoxin activity, directly triggering degranulation of mast cells, as well as increasing vascular

permeability and smooth muscle contraction. C5b initiates the membrane attack pathway, which results in the membrane attack complex (MAC), consisting of C5b, C6, C7, C8, and polymeric C9. MAC is the cytolytic endproduct of the complement cascade; it forms a transmembrane channel, which causes osmotic lysis of the target cell. Kupffer cells and other macrophage cell types help clear complement-coated pathogens. As part of the innate immune system, elements of the complement cascade can be found in species earlier than vertebrates, most recently in the protostome horseshoe crab species, putting the origins of the system back further than was previously thought.

n the classical pathway, C1 binds with its C1q subunits to Fc fragments (made of CH2 region) of IgG or IgM, which forms a complex with antigens. C4b and C3b are also able to bind to antigen-associated IgG or IgM, to its Fc portion.

Such immunoglobulin-mediated binding of the complement may be interpreted, as that the complement uses the ability of the immunoglobulin to detect and bind to non-self antigens as its guiding stick. The complement itself is able to bind non-self pathogens after detecting their pathogen-associated molecular patterns (PAMPs); however, utilizing specificity of antibody, complements are able to detect non-self enemies much more specifically. There must be mechanisms that complements bind to Ig but would not focus its function to Ig but to the antigen.

shows the classical and the alternative pathways with the late steps of complement activation schematically. Some components have a variety of binding sites. In the classical pathway, C4 binds to Ig-associated C1q and C1r2s2 enzyme cleaves C4 to C4b and 4a. C4b binds to C1q, antigen-associated Ig (specifically to its Fc portion), and even to the microbe surface. C3b binds to antigen-associated Ig and to the microbe surface. The ability of C3b to bind to antigen-associated Ig would work effectively against antigen-antibody immune complexes to make them soluble. In the figure, C2b refers to the larger of the C2 fragments.

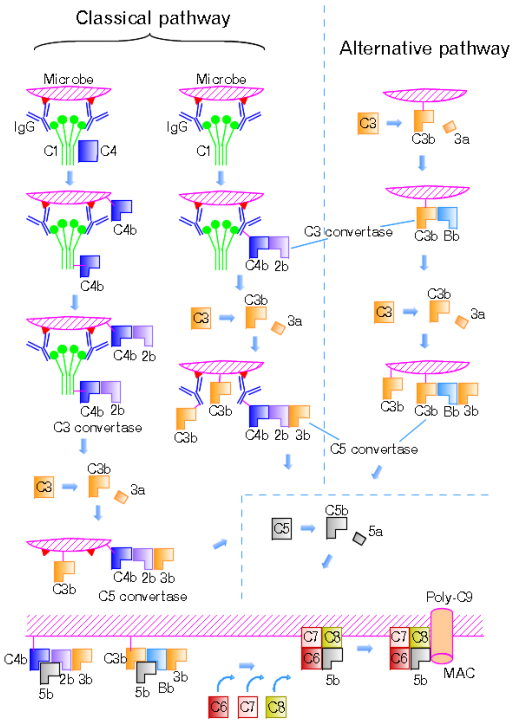

Figure: **Complement Pathways**: The classical and the alternative pathways with the late steps of complement activation.

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11.4B: Interferons

Learning Objectives

- Identify interferons and their effects

Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites, or tumor cells. IFNs belong to the large class of glycoproteins known as cytokines. Interferons are named after their ability to "interfere" with viral replication within host cells. IFNs have other functions: they activate immune cells, such as natural killer cells and macrophages, they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes, and they increase the ability of uninfected host cells to resist new infection by virus. Certain symptoms, such as aching muscles and fever, are related to the production of IFNs during infection.

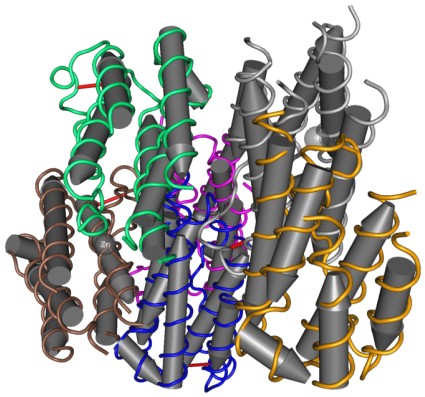

Figure: ***Interferon****: The molecular structure of human interferon-alpha.*

About ten distinct IFNs have been identified in mammals; seven of these have been described for humans. They are typically divided among three IFN classes: type I IFN, type II IFN, and type III IFN. IFNs belonging to all IFN classes are very important for fighting viral infections.

Based on the type of receptor through which they signal, human interferons have been classified into three major types:

- Interferon type I: All type I IFNs bind to a specific cell surface receptor complex, known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains. The type I interferons present in humans are IFN-α, IFN-β and IFN-ω.
- Interferon type II: These bind to IFNGR that consist of IFNGR1 and IFNGR2 chains. In humans this is IFN-γ.
- Interferon type III: These signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12). Acceptance of this classification is less universal than that of type I and type II, and unlike the other two, it is not currently included in *Medical Subject Headings*.

Effects of Interferons

All interferons share several common effects; they are antiviral agents and can fight tumors. As an infected cell dies from a cytolytic virus, viral particles are released that can infect nearby cells. In addition, interferons induce production of hundreds of other proteins—known collectively as interferon-stimulated genes (ISGs)—that have roles in combating viruses. They also limit viral spread by increasing p53 activity, which kills virus-infected cells by promoting apoptosis. The effect of IFN on p53 is also linked to its protective role against certain cancers. Another function of interferons is to upregulate major histocompatibility complex molecules, MHC I and MHC II, and increase immunoproteasome activity. Interferons, such as interferon gamma, directly activate other immune cells, such as macrophages and natural killer cells. Interferons can inflame the tongue and cause dysfunction in taste bud cells, restructuring or killing taste buds entirely.

By interacting with their specific receptors, IFNs activate signal transducer and activator of transcription (STAT) complexes. STATs are a family of transcription factors that regulate the expression of certain immune system genes. Some STATs are activated by both type I and type II IFNs. However, each IFN type can also activate unique STATs.

STAT activation initiates the most well-defined cell signaling pathway for all IFNs, the classical Janus kinase-STAT (JAK-STAT) signaling pathway. In this pathway, JAKs associate with IFN receptors and, following receptor engagement with IFN,

phosphorylate both STAT1 and STAT2. As a result, an IFN-stimulated gene factor 3 (ISGF3) complex forms—this contains STAT1, STAT2 and a third transcription factor called IRF9—and moves into the cell nucleus. Inside the nucleus, the ISGF3 complex binds to specific nucleotide sequences called IFN-stimulated response elements (ISREs) in the promoters of certain genes, known as IFN stimulated genes ISGs. Binding of ISGF3 and other transcriptional complexes activated by IFN signaling to these specific regulatory elements induces transcription of those genes. Interferome is a curated online database of ISGs (www.interferome.org). Additionally, STAT homodimers or heterodimers form from different combinations of STAT-1, -3, -4, -5, or -6 during IFN signaling; these dimers initiate gene transcription by binding to IFN-activated site (GAS) elements in gene promoters. Type I IFNs can induce expression of genes with either ISRE or GAS elements, but gene induction by type II IFN can occur only in the presence of a GAS element.

In addition to the JAK-STAT pathway, IFNs can activate several other signaling cascades. Both type I and type II IFNs activate a member of the CRK family of adaptor proteins called CRKL, a nuclear adaptor for STAT5 that also regulates signaling through the C3G/Rap1 pathway. Type I IFNs further activate p38 mitogen-activated protein kinase (MAP kinase) to induce gene transcription. Antiviral and antiproliferative effects specific to type I IFNs result from p38 MAP kinase signaling. The phosphatidylinositol 3-kinase (PI3K) signaling pathway is also regulated by both type I and type II IFNs. PI3K activates P70-S6 Kinase 1, an enzyme that increases protein synthesis and cell proliferation; phosphorylates of ribosomal protein s6, which is involved in protein synthesis; and phosphorylates a translational repressor protein called eukaryotic translation-initiation factor 4E-binding protein 1 (EIF4EBP1) in order to deactivate it.

Key Points

- Interferons are named after their ability to “interfere” with viral replication within host cells.
- IFNs are divided into three classes: type I IFN, type II IFN, and type III IFNs.
- IFNs activate immune cells (natural killer cells and macrophages), increase recognition of infection and tumor cells by up-regulating antigen presentation to T lymphocytes, and increase the ability of uninfected host cells to resist new infection by virus.

Key Terms

- **Interferons**: Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.
- **immune cells**: White blood cells, or leukocytes, are cells of the immune system involved in defending the body against both infectious disease and foreign materials.

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11.4C: Natural Killer Cells

Learning Objectives

- Describe natural killer cells

Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte critical to the innate immune system. The role NK cells play is similar to that of cytotoxic T cells in the vertebrate adaptive immune response. NK cells provide rapid responses to virally infected cells and to tumor formation, beginning around three days after infection. Typically immune cells detect MHC that is present on infected cell surfaces, triggering cytokine release and causing lysis or apoptosis. NK cells are unique, however, as they have the ability to recognize stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction. They were named “natural killers” because of the initial notion that they do not require activation in order to kill cells that are missing “self” markers of major histocompatibility complex (MHC) class 1.

NK cells are defined as large granular lymphocytes (LGL) and constitute the third kind of cell differentiated from the common lymphoid progenitor generating B and T lymphocytes. NK cells are known to differentiate and mature in the bone marrow, lymph node, spleen, tonsils, and thymus, where they then enter into the circulation. NK cells differ from Natural Killer T cells (NKT) phenotypically, by origin, and by respective effector functions. Often NKT cell activity promotes NK cell activity by secreting IFNγ. In contrast to NKT cells, NK cells do not express T-cell antigen receptors (TCR) or Pan T marker CD3 or surface immunoglobulins (Ig) B cell receptors, but they usually express the surface markers CD16 (FcγRIII) and CD56 in humans, NK1.1 or NK1.2 in C57BL/6 mice. Up to 80% of human NK cells also express CD8.

Mechanism

NK cells paralyze target cells using the cytolytic protein perforin and a variety of protease enzymes. An NK cell will first use perforin to create pores in a target cell, allowing it to inject granzymes through an aqueous channel. The granzymes then break down the target cell, inducing death by either apoptosis or osmotic cell lysis.

NK cells also alert the greater immune system by secreting chemicals that are taken as a message that a threat has arrived.



Figure: ***Schematic diagram indicating the complementary activities of cytotoxic T-cells and NK cells.***: *Schematic diagram indicating the complementary activities of cytotoxic T-cells and NK cells.*

Natural Killer Cells Play Other Roles

Natural killer cells are not only effectors of innate immunity; recent research has also uncovered information on both activating and inhibitory NK cell receptors, which play roles in maintaining self-tolerance and sustaining NK cell activity. NK cells also play a role in the adaptive immune response. Numerous experiments have demonstrated their ability to adjust to the immediate environment and formulate antigen-specific immunological memory, which is fundamental for responding to secondary infections with the same antigen. The ability for NK cells to act in both innate and adaptive immune response is becoming increasingly important in research utilizing NK cell activity in potential cancer therapies.

NK cell receptors can also be differentiated based on function. Natural cytotoxicity receptors directly induce apoptosis after binding to ligands that directly indicate infection of a cell. The MHC dependent receptors (described above) use an alternate pathway to induce apoptosis in infected cells. Natural killer cell activation is determined by the balance of inhibitory and activating

receptor stimulation—for example, if the inhibitory receptor signaling is more prominent, then NK cell activity will be inhibited. Similarly, if the activating signal is dominant, then NK cell activation will result.

Functions of NK cells include: Cytolytic Granule Mediated Cell Apoptosis; Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC); Cytokine induced NK and CTL activation; Missing 'self' hypothesis; Tumor cell surveillance; NK cell function in adaptive response; NK cell function in pregnancy; and NK cell evasion by tumor cells.

Key Points

- NK cells are defined as large granular lymphocytes (LGL).
- NK cells constitute the third kind of cells differentiated from the common lymphoid progenitor generating B and T lymphocytes.
- NK cells provide rapid responses to virally infected cells and respond to tumor formation, acting at around 3 days after infection.

Key Terms

- **Natural killer cells (or NK cells)**: Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte critical to the innate immune system. The role NK cells play is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response.
- **lymphocyte**: A type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-lymphocytes, which produce antibodies in the humoral immune response, T-lymphocytes, which participate in the cell-mediated immune response, and the null group, which contains natural killer cells, cytotoxic cells that participate in the innate immune response.
- **innate immune system**: This is the initial line of defense that entails a cascade of cells and mechanisms that protect the host from infection by different organisms in an indeterminate pattern.

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11.4D: Toll-Like Receptors

Learning Objectives

- Summarize Toll-like receptors

Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system as well as the digestive system. They are single, membrane-spanning, non-catalytic receptors that recognize structurally conserved molecules derived from microbes. Once these microbes have breached physical barriers such as the skin or intestinal tract mucosa, they are recognized by TLRs, which activate immune cell responses.

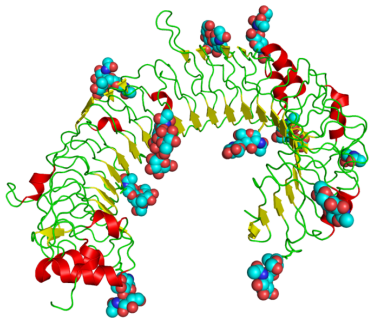

Figure: **TLR3**: The curved leucine-rich repeat region of Toll-like receptors, represented here by TLR3

TLRs are a type of pattern recognition receptor (PRR) and recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs). TLRs together with the Interleukin-1 receptors form a receptor superfamily, known as the “Interleukin-1 Receptor/Toll-Like Receptor Superfamily”; all members of this family have in common a so-called TIR (Toll-IL-1 receptor) domain.

Because of the specificity of Toll-like receptors (and other innate immune receptors) they cannot easily be changed in the course of evolution, these receptors recognize molecules that are constantly associated with threats (i.e., pathogen or cell stress) and are highly specific to these threats (i.e., cannot be mistaken for self molecules). Pathogen-associated molecules that meet this requirement are usually critical to the pathogen’s function and cannot be eliminated or changed through mutation; they are said to be evolutionarily conserved. Well-conserved features in pathogens include bacterial cell-surface lipopolysaccharides (LPS), lipoproteins, lipopeptides, and lipoarabinomannan; proteins such as flagellin from bacterial flagella; double-stranded RNA of viruses; or the unmethylated CpG islands of bacterial and viral DNA; and certain other RNA and DNA. For most of the TLRs, ligand recognition specificity has now been established by gene targeting (also known as “gene knockout”): a technique by which individual genes may be selectively deleted in mice. See the table below for a summary of known TLR ligands.

TLRs are believed to function as dimers. Though most TLRs appear to function as homodimers, TLR2 forms heterodimers with TLR1 or TLR6, each dimer having a different ligand specificity. TLRs may also depend on other co-receptors for full ligand sensitivity, such as in the case of TLR4’s recognition of LPS, which requires MD-2. CD14 and LPS-Binding Protein (LBP) are known to facilitate the presentation of LPS to MD-2.

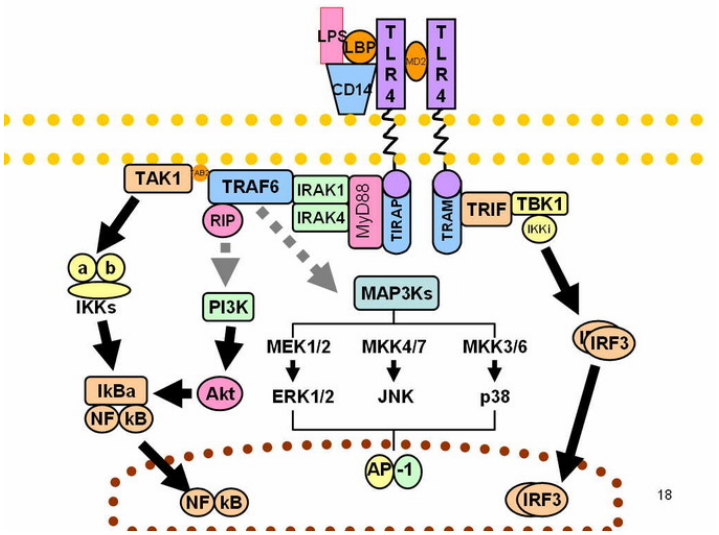

Figure: **Signaling pathway**: Signaling pathway of Toll-like receptors. Dashed grey lines represent unknown associations.

The adapter proteins and kinases that mediate TLR signaling have also been targeted. In addition, random germline mutagenesis with ENU has been used to decipher the TLR signaling pathways. When activated, TLRs recruit adapter molecules within the cytoplasm of cells in order to propagate a signal. Four adapter molecules are known to be involved in signaling. These proteins are known as MyD88, Tirap (also called Mal), Trif, and Tram.

TLR signaling is divided into two distinct signaling pathways, the MyD88-dependent and TRIF-dependent pathway. The MyD88-dependent response occurs on dimerization of the TLR receptor, and is utilized by every TLR except TLR3. Its primary effect is activation of NFκB. Ligand binding and conformational change that occurs in the receptor recruits the adaptor protein MyD88, a member of the TIR family. MyD88 then recruits IRAK 4, IRAK1 and IRAK2. IRAK kinases then phosphorylate and activate the protein TRAF6, which in turn polyubiquinates the protein TAK1, as well as itself in order to facilitate binding to IKKβ. On binding, TAK1 phosphorylates IKKβ, which then phosphorylates IκB causing its degradation and allowing NFκB to diffuse into the cell nucleus and activate transcription.

Both TRL3 and TRL4 utilize the TRIF-dependent pathway, which is triggered by dsRNA and LPS, respectively. For TRL3, dsRNA leads to activation of the receptor, recruiting the adaptor TRIF. TRIF activates the kinases TBK1 and RIP1, which creates a branch in the signaling pathway. The TRIF/TBK1 signaling complex phosphorylates IRF3 allowing its translocation into the nucleus and production of Type I interferons. Meanwhile, activation of RIP1 causes the polyubiquination and activation of TAK1 and NFκB transcription in the same manner as the MyD88-dependent pathway.

TLR signaling ultimately leads to the induction or suppression of genes that orchestrate the inflammatory response. In all, thousands of genes are activated by TLR signaling, and collectively, the TLRs constitute one of the most pleiotropic yet tightly regulated gateways for gene modulation.

Toll-like receptors bind and become activated by different ligands, which, in turn, are located on different types of organisms or structures. They also have different adapters to respond to activation and are located sometimes at the cell surface and sometimes to internal cell compartments.

Key Points

- TLRs are a type of pattern recognition receptor (PRR).
- TLRs recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs).
- TLR signaling is divided into two distinct signaling pathways, the MyD88-dependent and TRIF-dependent pathway.

Key Terms

- **Toll-like receptor**: Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system as well as the digestive system. They are single, membrane-spanning, non-catalytic receptors that recognize structurally conserved molecules derived from microbes.

- **innate immune system**: This is the initial line of defense that entails a cascade of cells and mechanisms that protect the host from infection by different organisms in an indeterminate pattern.
- **signaling pathway**: Signal pathways occurs when an extracellular signaling molecule activates a cell surface receptor. In turn, this receptor alters intracellular molecules creating a response. There are two stages in this process:A signaling molecule activates a specific receptor protein on the cell membrane.A second messenger transmits the signal into the cell, eliciting a physiological response.In either step, the signal can be amplified. Thus, one signaling molecule can cause many responses.

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11.4E: Iron-Binding Proteins

Iron binding proteins of the innate immune system include lactoferrin and transferrins.

Learning Objectives

- Describe Iron-Binding proteins

Key Points

- Lactoferrin (LF), also known as lactotransferrin (LTF), is a multifunctional protein of the transferrin family.
- Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa that is widely represented in various secretory fluids such as milk, saliva, tears, and nasal secretions.
- Transferrins are iron -binding blood plasma glycoproteins that control the level of free iron in biological fluids.

Key Terms

- **transferrin**: A glycoprotein, a beta globulin, in blood serum that combines with and transports iron
- **Lactoferrin**: Lactoferrin (LF), also known as lactotransferrin (LTF), is a multifunctional protein of the transferrin family. Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa. It is widely represented in various secretory fluids such as milk, saliva, tears, and nasal secretions.
- **iron**: Iron is a chemical element with the symbol Fe (from Latin: ferrum) and atomic number 26. It is a metal in the first transition series.

Iron-binding proteins are proteins generally used to play roles in metabolism. They are carrier proteins (those used to move ions and molecules across membranes) and more generally metalloproteins (those which contain a metal ion cofactor). Iron-binding proteins are serum proteins, found in the blood, and as their name suggests, are used to bind and transport iron.

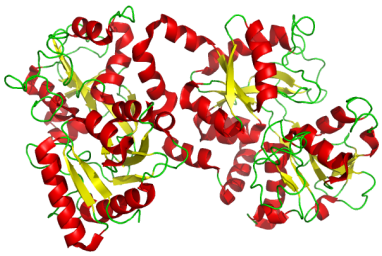

Figure: **Lactoferrin**: Richardson diagram of recombinant human lactoferrin. Based on PDB (Protein Data Bank) 1b0l

Lactoferrin (LF), also known as lactotransferrin (LTF), is a multifunctional protein of the transferrin family. Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa. It is widely represented in various secretory fluids such as milk, saliva, tears, and nasal secretions. Lactoferrin is also present in secondary granules of PMN (Polymorphonucler neutrophil) and is secreted by some acinar cells. Lactoferrin can be purified from milk or produced recombinantly. Human colostrum (“first milk”) has the highest concentration, followed by human milk, and then cow milk (150 mg/L).

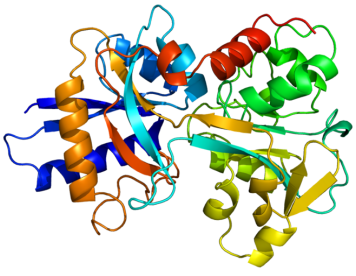

Figure: **Transferrin**: PDB (Protein Data Bank) rendering based on 1a8e.

Lactoferrin is one of the components of the immune system of the body. It has antimicrobial activity (bacteriocide, fungicide) and is part of the innate defense, mainly at mucoses. In particular, lactoferrin provides antibacterial activity to human infants.

Lactoferrin interacts with DNA and RNA, polysaccharides and heparin, and shows some of its biological functions in complexes with these ligands.

Transferrins are iron-binding blood plasma glycoproteins that control the level of free iron in biological fluids. Human transferrin is encoded by the TF gene. Transferrin glycoproteins bind iron very tightly, but reversibly. Although iron bound to transferrin is less than 0.1% (4 mg) of the total body iron, it is the most important iron pool, with the highest rate of turnover (25 mg/24 h). Transferrin has a molecular weight of around 80 KDa and contains two specific high- affinity Fe(III) binding sites. The affinity of transferrin for Fe(III) is extremely high (1023 M^{-1} at pH 7.4), but decreases progressively with decreasing pH below neutrality. When not bound to iron, it is known as “apotransferrin” (see also apoprotein).

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11.4F: Antimicrobial Peptides

Antimicrobial peptides are an evolutionarily conserved component of the innate immune response and are found among all classes of life.

Learning Objectives

- Describe the role of antimicrobial peptides in host defense

Key Points

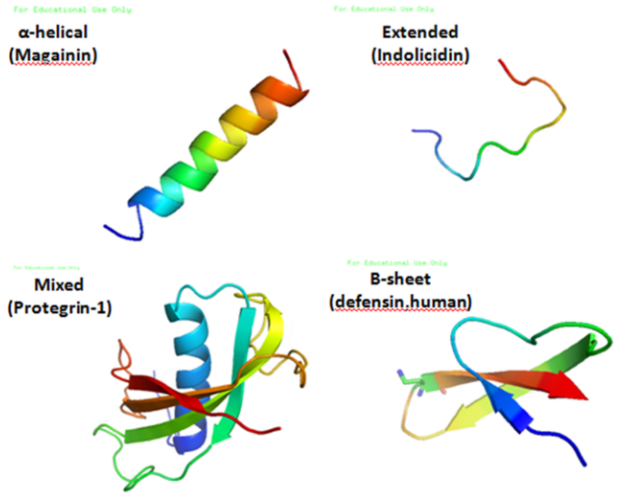
- Antimicrobial peptides are a unique and diverse group of molecules, which are divided into subgroups on the basis of their amino acid composition and structure.
- The modes of action by which antimicrobial peptides kill bacteria is varied and includes disrupting membranes, interfering with metabolism, and targeting cytoplasmic components.
- Antimicrobial peptides have been demonstrated to have a number of immunomodulatory functions that may be involved in the clearance of infection.

Key Terms

- **antimicrobial peptide**: Antimicrobial peptides (also called host defense peptides) are an evolutionarily conserved component of the innate immune response and are found among all classes of life.
- **innate immune**: The innate immune system, also known as non-specific immune system and first line of defense, comprises the cells and mechanisms that defend the host from infection by other organisms in a non-specific manner. This means that the cells of the innate system recognize and respond to pathogens in a generic way, but unlike the adaptive immune system, it does not confer long-lasting or protective immunity to the host.
- **molecules**: A molecule is an electrically neutral group of two or more atoms held together by covalent chemical bonds. Molecules are distinguished from ions by their lack of electrical charge. However, in quantum physics, organic chemistry, and biochemistry, the term molecule is often used less strictly, also being applied to polyatomic ions.

Antimicrobial peptides (also called host defense peptides) are an evolutionarily conserved component of the innate immune response and are found among all classes of life. Fundamental differences exist between prokaryotic and eukaryotic cells that may represent targets for antimicrobial peptides. These peptides are potent, broad spectrum antibiotics which demonstrate potential as novel therapeutic agents. Antimicrobial peptides have been demonstrated to kill Gram negative and Gram positive bacteria (including strains that are resistant to conventional antibiotics), mycobacteria (including Mycobacterium tuberculosis), enveloped viruses, fungi and even transformed or cancerous cells. Unlike the majority of conventional antibiotics, it appears as though antimicrobial peptides may also have the ability to enhance immunity by functioning as immunomodulators.

Antimicrobial peptides are a unique and diverse group of molecules, which are divided into subgroups on the basis of their amino acid composition and structure. Antimicrobial peptides generally consist of between 12 and 50 amino acids. These peptides include two or more positively charged residues provided by arginine, lysine or, in acidic environments, histidine, and a large proportion (generally >50%) of hydrophobic residues. The secondary structures of these molecules follow 4 themes, including:



Various AMPs: These are various antimicrobial peptide structures.

1. α-helical
2. β-stranded due to the presence of 2 or more disulfide bonds
3. β-hairpin or loop due to the presence of a single disulfide bond and/or cyclization of the peptide chain
4. Extended

Many of these peptides are unstructured in free solution, and fold into their final configuration upon partitioning into biological membranes. It contains hydrophilic amino acid residues aligned along one side and hydrophobic amino acid residues aligned along the opposite side of a helical molecule. This amphipathicity of the antimicrobial peptides allows the partition of the membrane lipid bilayer. The ability to associate with membranes is a definitive feature of antimicrobial peptides, although membrane permeabilisation is not necessary. These peptides have a variety of antimicrobial activities ranging from membrane permeabilization to action on a range of cytoplasmic targets.

The modes of action by which antimicrobial peptides kill bacteria is varied and includes disrupting membranes, interfering with metabolism, and targeting cytoplasmic components. The initial contact between the peptide and the target organism is electrostatic, as most bacterial surfaces are anionic, or hydrophobic, such as in the antimicrobial peptide Piscidin. Their amino acid composition, amphipathicity, cationic charge, and size allow them to attach to and insert into membrane bilayers to form pores by ‘barrel-stave’, ‘carpet’ or ‘toroidal-pore’ mechanisms. Alternately, they may penetrate into the cell to bind intracellular molecules which are crucial to cell living. Intracellular binding models include inhibition of cell wall synthesis, alteration of the cytoplasmic membrane, activation of autolysin, inhibition of DNA, RNA, and protein synthesis, and inhibition of certain enzymes. However, in many cases, the exact mechanism of killing is not known. One emerging technique for the study of such mechanisms is dual polarisation interferometry. In contrast to many conventional antibiotics these peptides appear to be bacteriocidal (bacteria killing) instead of bacteriostatic (bacteria growth inhibiting). In general the antimicrobial activity of these peptides is determined by measuring the minimal inhibitory concentration (MIC), which is the lowest concentration of drug that inhibits bacterial growth.

In addition to killing bacteria directly, they have been demonstrated to have a number of immunomodulatory functions that may be involved in the clearance of infection, including the ability to:

- Alter host gene expression
- Act as chemokines and/or induce chemokine production,
- Inhibit lipopolysaccharide induced pro-inflammatory cytokine production
- Promote wound healing
- Modulate the responses of dendritic cells and cells of the adaptive immune response

Animal models indicate that host defense peptides are crucial for both prevention and clearance of infection. It appears as though many peptides initially isolated and termed as “antimicrobial peptides” have been shown to have more significant alternative functions in vivo (e.g. hepcidin).

Several methods have been used to determine the mechanisms of antimicrobial peptide activity. In particular, solid-state NMR studies have provided an atomic-level resolution explanation of membrane disruption by antimicrobial peptides.

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11.4G: The Complement System and Heart Disease

In autoimmune heart diseases, the body's immune defense system mistakes its own cardiac antigens as foreign, and attacks them.

Learning Objectives

- Identify autoimmune heart diseases

Key Points

- The commonest form of autoimmune heart disease is rheumatic heart disease, or rheumatic fever.
- The typical mechanism of autoimmunity involves auto-toxic T-lymphocyte, and the complement system.
- Inflammatory damage leads to the following: pericarditis, myocarditis, and endocarditis.

Key Terms

- **autoimmune**: Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmunity is often caused by a lack of germ development of a target body, and as such the immune response acts against its own cells and tissues.
- **immune**: Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion. In other words, it is the capability of the body to resist harmful microbes from entering it. Immunity involves both specific and non-specific components.
- **antigen**: A substance that induces an immune response, usually foreign.

Causes

Autoimmune heart diseases result when the body's own immune defense system mistakes cardiac antigens as foreign, and attacks them, leading to inflammation of the heart as a whole, or in parts. The most common form of autoimmune heart disease is rheumatic heart disease, or rheumatic fever.

A typical mechanism of autoimmunity is autoantibodies, or auto-toxic T-lymphocyte mediated tissue destruction. The process is aided by neutrophils, the complement system, and tumor necrosis factor alpha.

Aetiologically, autoimmune heart disease is most commonly seen in children with a history of sore throat caused by a streptococcal infection. This is similar to the post-streptococcal glomerulonephritis. Here, the anti-bacterial antibodies cross react with the heart antigens causing inflammation.

Pericarditis, Myocarditis, and Endocarditis

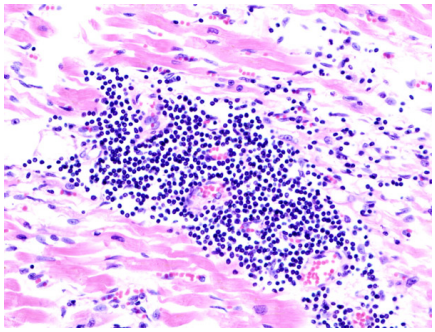

Figure: **Viral myocarditis**: Histopathological image of myocarditis at autopsy in a patient with acute onset of congestive heart failure

Inflammatory damage can lead to pericarditis, myocarditis, and endocarditis.

Pericarditis: Here the pericardium gets inflamed. Acutely, it can cause pericardial effusion leading to cardiac tamponade and death. After healing, there may be fibrosis and adhesion of the pericardium with the heart, leading to constriction of the heart and reduced cardiac function.

Myocarditis: Here the muscle bulk of the heart gets inflamed. Inflamed muscles have reduced functional capacity. This may be fatal if left untreated, as is in a case of pancarditis. On healing, there will be fibrosis and reduced functional capacity.

Endocarditis: Here the inner lining of the heart is inflamed, including the heart valves. This may cause a valve prolapse, adhesion of the adjacent cusps, of these valves, and occlusion of the flow tracts of blood through the heart, which causes disease known as valve stenosis.

Treatment

Specific clinical manifestations depend on the amount of inflammation. Therapy will involve intensive cardiac care and immunosuppressives, including corticosteroids, which are helpful in the acute stage of the disease. The chronic phase consists of mainly debility control and supportive care options.

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SECTION OVERVIEW

11.5: The Adaptive Immune Response

Topic hierarchy

11.5A: Humoral Immune Response

11.5B: Development of the Dual Lymphocyte System

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11.5A: Humoral Immune Response

The humoral immune response defends against pathogens that are free in the blood by using antibodies against pathogen-specific antigens.

Learning Objectives

- Summarize the humoral immune response

Key Points

- Antigens are proteins and other macromolecules that bind to a specific antibody and are used by the immune system to recognize pathogens.
- B cells express receptors (BCRs) on their membrane which contain antibodies; these antibodies allow B cells to detect pathogens and release further antibodies to fight the infection.
- Antibodies fight infections in three ways: they mark pathogens for destruction by phagocytic cells in a process known as opsonization, they coat key sites on pathogens necessary for infection, and they induce the complement cascade to occur against antibody-bound pathogens.
- Once the adaptive immune response has encountered an antigen, B cells will divide to produce plasma cells, which rapidly secrete antibodies to that antigen in a process called active immunity.

Key Terms

- **antibody**: a protein produced by B-lymphocytes that binds to a specific antigen
- **opsonize**: to make (bacteria or other cells) more susceptible to the action of phagocytes by use of opsonins
- **MHC**: an acronym for major histocompatibility complex; these extracellular protein receptors display antigens derived from extracellular (class I) or intracellular (class II) proteins and other biomolecules

The humoral immune response fights pathogens that are free in the bodily fluids, or “humours”. It relies on antigens (which are also often free in the humours) to detect these pathogens. An antigen is a biomolecule, such as a protein or sugar, that binds to a specific antibody. An antibody/antigen interaction may stimulate an immune response. Not every biomolecule is antigenic and not all antigens produce an immune response. B cells are the major cell type involved in the humoral immune response. When a foreign antigen (one coming from a pathogen, for example) is detected, B cells in the body that recognize that antigen will begin to produce antibodies as a means of fighting off the foreign invader.

B cell maturation

During maturation, B cells gain antigen receptor molecules, termed B cell receptors (BCRs), which are displayed in large numbers, extracellularly on their membrane. These membrane-bound protein complexes contain antibodies, which enable specific antigen recognition. Each B cell initially produced has only one kind of antibody (antigen receptor), which makes every B cell unique. It is the immense number of B cells in the body, each of which produces a unique antibody, that allows the immune system to detect such a wide variety of pathogenic antigens. B cells containing antibodies that recognize “self” antigens are destroyed before they can mature, preventing the immune system from attacking the host. Once B cells mature in the bone marrow, they migrate to lymph nodes or other lymphatic organs, where they may begin to encounter pathogens.

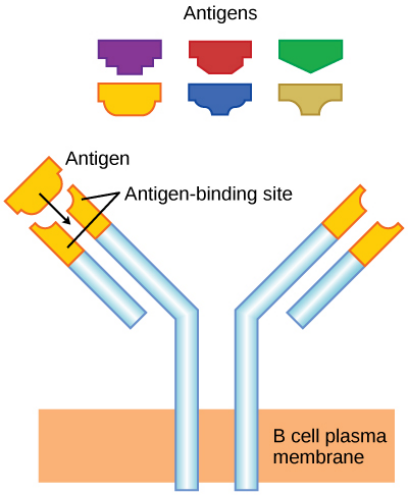

Figure: **B cell receptors**: B cell receptors, containing antibodies (termed antigen-binding site in the picture) are embedded in the membranes of B cells and bind a variety of antigens through their variable regions.

B cell activation

When a B cell encounters the antigen that binds to its receptor, the antigen molecule is brought into the cell by endocytosis, reappearing on the surface of the cell bound to an MHC class II molecule. When this process is complete, the B cell is sensitized. In most cases, the sensitized B cell must then encounter a specific kind of T cell, called a helper T cell, before it is activated. This activation of the helper T cell occurs when a dendritic cell presents an antigen on its MHC II molecule, allowing the T cell to recognize it and mature.

The helper T cell binds to the antigen-MHC class II complex and is induced to release cytokines that induce the B cell to divide rapidly, making thousands of identical (clonal) cells. These daughter cells become either plasma cells or memory B cells. The memory B cells remain inactive at this point. A later encounter with the antigen, caused by a reinfection by the same bacteria or virus, will result in them dividing into a new population of plasma cells. The plasma cells, on the other hand, produce and secrete large quantities, up to 100 million molecules per hour, of antibody molecules. An antibody, also known as an immunoglobulin (Ig), is a protein that is produced by plasma cells after stimulation by an antigen. Antibodies are the agents of humoral immunity. Antibodies occur in the blood, in gastric and mucus secretions, and in breast milk. Antibodies in these bodily fluids can bind pathogens and mark them for destruction by phagocytes before they are able to infect cells.

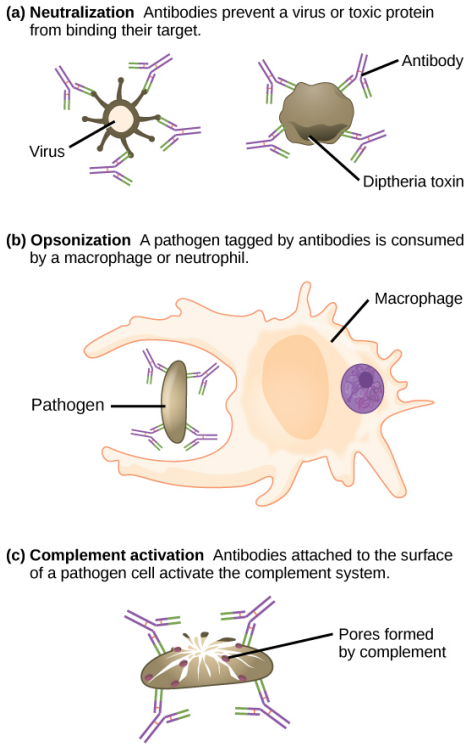

Figure: **Methods by which antibodies inhibit infection**: Antibodies may inhibit infection by (a) preventing the antigen from binding its target, (b) tagging a pathogen for destruction by macrophages or neutrophils, or (c) activating the complement cascade.

Antibodies

These antibodies circulate in the blood stream and lymphatic system, binding with the antigen whenever it is encountered. The binding can fight infection in several ways. Antibodies can bind to viruses or bacteria, which interferes with the chemical interactions required for them to infect or bind to other cells. The antibodies may create bridges between different particles containing antigenic sites, clumping them all together and preventing their proper functioning. Antibody neutralization can prevent pathogens from entering and infecting host cells. The neutralized antibody-coated pathogens can then be filtered by the spleen to be eliminated in urine or feces. The antigen-antibody complex stimulates the complement system described previously, destroying the cell bearing the antigen. Antibodies also opsonize pathogen cells, wherein they mark them for destruction by phagocytic cells, such as macrophages or neutrophils. Additionally, antibodies stimulate inflammation, while their presence in mucus and on the skin prevents pathogen attack.

The production of antibodies by plasma cells in response to an antigen is called active immunity. This describes the host's active response of the immune system to an infection or to a vaccination. There is also a passive immune response wherein antibodies are introduced into the host from an outside source, instead of the individual's own plasma cells. For example, antibodies circulating in a pregnant woman's body move across the placenta into the developing fetus. The child benefits from the presence of these antibodies for up to several months after birth. In addition, a passive immune response is possible by injecting antibodies into an individual in the form of an antivenom to a snake-bite toxin or antibodies in blood serum to help fight a hepatitis infection, giving immediate relief.

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11.5B: Development of the Dual Lymphocyte System

Lymphocytes originate from a common progenitor in a process known as hematopoeisis.

Learning Objectives

- Examine dual lymphocyte development

Key Points

- B cells and T cells are the major types of lymphocytes.
- B cells mature into B lymphocytes in the bone marrow, while T cells migrate to, and mature in, a distinct organ called the thymus.
- Following maturation, the lymphocytes enter the circulation and peripheral lymphoid organs (e.g. the spleen and lymph nodes) where they survey for invading pathogens and/or tumor cells.
- The lymphocytes involved in adaptive immunity (i.e. B and T cells) differentiate further after exposure to an antigen to form effector and memory lymphocytes.

Key Terms

- **lymphocyte**: A type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-lymphocytes, which produce antibodies in the humoral immune response, T-lymphocytes, which participate in the cell-mediated immune response, and the null group, which contains natural killer cells, cytotoxic cells that participate in the innate immune response.
- **leukocyte**: A white blood cell.
- **haematopoiesis**: Hematopoeisis is the formation of blood cellular components from a common progenitor stem cell.

The cells of the adaptive immune system are a type of leukocyte, called a lymphocyte. The human body has about 2 trillion lymphocytes, constituting 20-40% of white blood cells (WBCs); their total mass is about the same as the brain or liver. The peripheral blood contains 20–50% of circulating lymphocytes; the rest move within the lymphatic system. B cells and T cells are the major types of lymphocytes.

B Cell and T Cell Differentiation

Mammalian stem cells differentiate into several kinds of blood cell within the bone marrow. This process is called haematopoiesis. During this process, all lymphocytes originate from a common lymphoid progenitor before differentiating into their distinct lymphocyte types. The differentiation of lymphocytes into distinguishable types follows various pathways in a hierarchical fashion as well as in a more plastic fashion. The formation of lymphocytes is known as lymphopoiesis. B cells mature into B lymphocytes in the bone marrow, while T cells migrate to, and mature in, a distinct organ called the thymus. Following maturation, the lymphocytes enter the circulation and peripheral lymphoid organs (e.g. the spleen and lymph nodes) where they survey for invading pathogens and/or tumor cells.

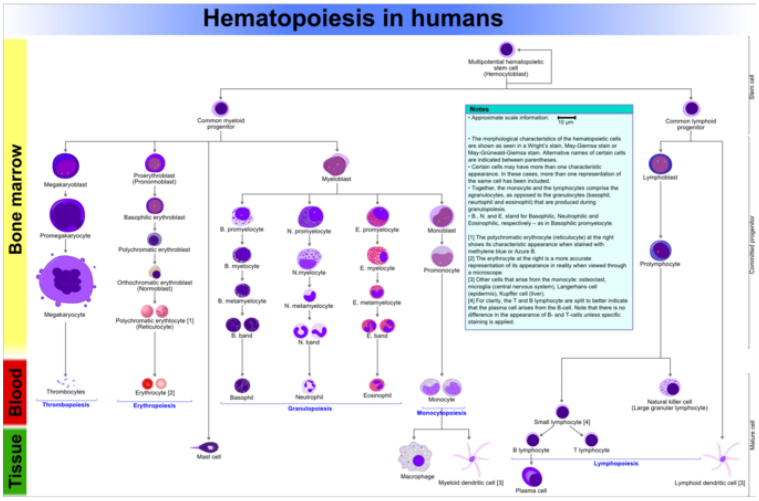

Figure: **Hematopoeisis in humans**: Mammalian stem cells differentiate into several kinds of blood cell within the bone marrow. This process is called haematopoiesis. All lymphocytes originate during this process from a common lymphoid progenitor before differentiating into their distinct lymphocyte types.

Further Differentiation

The lymphocytes involved in adaptive immunity (i.e. B and T cells) differentiate further after exposure to an antigen; they form effector and memory lymphocytes. Effector lymphocytes function to eliminate the antigen, either by releasing antibodies (in the case of B cells), cytotoxic granules (cytotoxic T cells) or by signaling to other cells of the immune system (helper T cells). Memory cells remain in the peripheral tissues and circulation for an extended time ready to respond to the same antigen upon future exposure.

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SECTION OVERVIEW

11.6: Antigens and Antibodies

Topic hierarchy

11.6A: Immunodeficiency

11.6B: Antibody Functions

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11.6A: Immunodeficiency

Immunodeficiency occurs when the immune system cannot appropriately respond to infections.

Learning Objectives

- Explain the problems associated with immunodeficiency

Key Points

- If a pathogen is allowed to proliferate to certain levels, the immune system can become overwhelmed; immunodeficiency occurs when the immune system fails to respond sufficiently to a pathogen.
- Immunodeficiency can be caused by many factors, including certain pathogens, malnutrition, chemical exposure, radiation exposure, or even extreme stress.
- HIV is a virus that causes immunodeficiency by infecting helper T cells, causing cytotoxic T cells to destroy them.

Key Terms

- **phagocyte**: a cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria, and waste materials
- **lysis**: the disintegration or destruction of cells
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold to replicate or proliferate to high enough levels that the immune system becomes overwhelmed, leading to immunodeficiency; it may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or, possibly, by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes, elevating an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

HIV/AIDS

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system. The person has a high probability of becoming infected, including from opportunistic infections and tumors that do not usually affect people who have working immune systems.

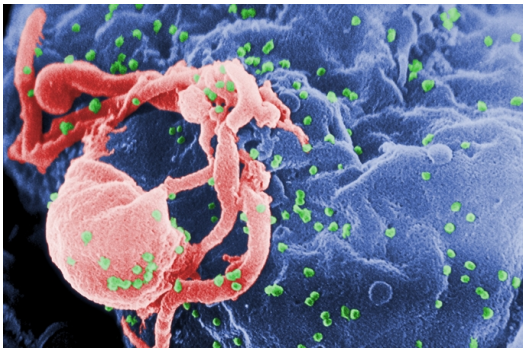

Figure: **Image of HIV: scanning electron micrograph of HIV-1 budding (in green, color added) from cultured lymphocyte**: Multiple round bumps on cell surface represent sites of assembly and budding of HIV. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells, cells that are or will become helper T cells. The acute viremia, or spreading of the virus, is almost invariably associated with activation of CD8+ T cells (which kill HIV-infected cells) and, subsequently, with antibody production. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

Ultimately, HIV causes AIDS by depleting CD4+ T cells (helper T cells). This weakens the immune system, allowing opportunistic infections. T cells are essential to the immune response; without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis (programmed cell death) may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

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11.6B: Antibody Functions

Antibodies, part of the humoral immune response, are involved in pathogen detection and neutralization.

Learning Objectives

- Differentiate among affinity, avidity, and cross-reactivity in antibodies

Key Points

- Antibodies are produced by plasma cells, but, once secreted, can act independently against extracellular pathogen and toxins.
- Antibodies bind to specific antigens on pathogens; this binding can inhibit pathogen infectivity by blocking key extracellular sites, such as receptors involved in host cell entry.
- Antibodies can also induce the innate immune response to destroy a pathogen, by activating phagocytes such as macrophages or neutrophils, which are attracted to antibody-bound cells.
- Affinity describes how strongly a single antibody binds a given antigen, while avidity describes the binding of a multimeric antibody to multiple antigens.
- A multimeric antibody may have individual arms with low affinity, but have high overall avidity due to synergistic effects between binding sites.
- Cross reactivity occurs when an antibody binds to a different-but-similar antigen than the one for which it was raised; this can increase pathogen resistance or result in an autoimmune reaction.

Key Terms

- **avidity**: the measure of the synergism of the strength individual interactions between proteins
- **affinity**: the attraction between an antibody and an antigen

Antibody Functions

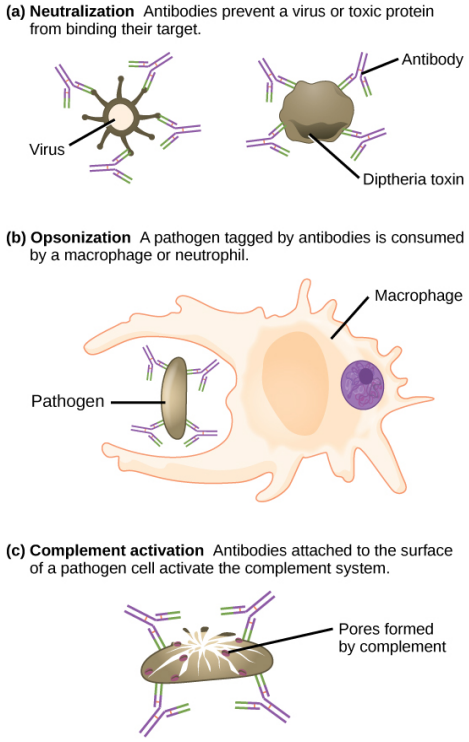

Figure: **Mechanisms of antibody action**: Antibodies may inhibit infection by (a) preventing the antigen from binding to its target, (b) tagging a pathogen for destruction by macrophages or neutrophils, or (c) activating the complement cascade.

Differentiated plasma cells are crucial players in the humoral immunity response. The antibodies they secrete are particularly significant against extracellular pathogens and toxins. Once secreted, antibodies circulate freely and act independently of plasma cells. Sometimes, antibodies can be transferred from one individual to another. For instance, a person who has recently produced a

successful immune response against a particular disease agent can donate blood to a non-immune recipient, confering temporary immunity through antibodies in the donor's blood serum. This phenomenon, called passive immunity, also occurs naturally during breastfeeding, which makes breastfed infants highly resistant to infections during the first few months of life.

Antibodies coat extracellular pathogens and neutralize them by blocking key sites on the pathogen that enhance their infectivity, such as receptors that "dock" pathogens on host cells. Antibody neutralization can prevent pathogens from entering and infecting host cells, as opposed to the cytotoxic T-cell-mediated approach of killing cells that are already infected to prevent progression of an established infection. The neutralized antibody-coated pathogens can then be filtered by the spleen and eliminated in urine or feces.

Antibodies also mark pathogens for destruction by phagocytic cells, such as macrophages or neutrophils, because they are highly attracted to macromolecules complexed with antibodies. Phagocytic enhancement by antibodies is called opsonization. In another process, complement fixation, IgM and IgG in serum bind to antigens, providing docking sites onto which sequential complement proteins can bind. The combination of antibodies and complement enhances opsonization even further, promoting rapid clearing of pathogens.

Affinity, avidity, and cross reactivity

Not all antibodies bind with the same strength, specificity, and stability. In fact, antibodies exhibit different affinities (attraction) depending on the molecular complementarity between antigen and antibody molecules. An antibody with a higher affinity for a particular antigen would bind more strongly and stably. It would be expected to present a more challenging defense against the pathogen corresponding to the specific antigen.

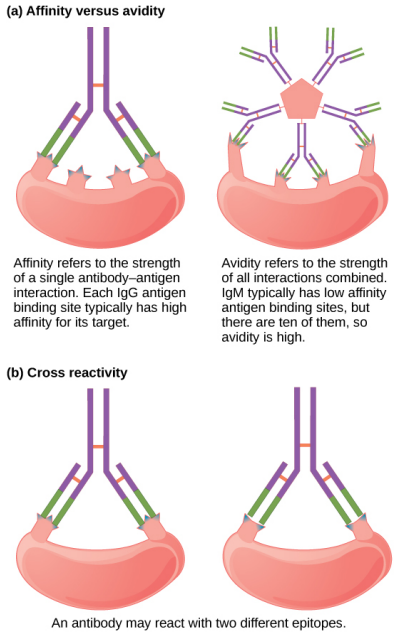

Figure: **Antibody affinity, avidity, and cross reactivity**: (a) Affinity refers to the strength of single interactions between antigen and antibody, while avidity refers to the strength of all interactions combined. (b) An antibody may cross-react with different epitopes.

The term avidity describes binding by antibody classes that are secreted as joined, multivalent structures (such as IgM and IgA). Although avidity measures the strength of binding, just as affinity does, the avidity is not simply the sum of the affinities of the antibodies in a multimeric structure. The avidity depends on the number of identical binding sites on the antigen being detected, as well as other physical and chemical factors. Typically, multimeric antibodies, such as pentameric IgM, are classified as having lower affinity than monomeric antibodies, but high avidity. Essentially, the fact that multimeric antibodies can bind many antigens simultaneously balances their slightly-lower-binding strength for each antibody/antigen interaction.

Antibodies secreted after binding to one epitope on an antigen may exhibit cross reactivity for the same or similar epitopes on different antigens. Cross reactivity occurs when an antibody binds not to the antigen that elicited its synthesis and secretion, but to a different antigen. Because an epitope corresponds to such a small region (the surface area of about four to six amino acids), it is possible for different macromolecules to exhibit the same molecular identities and orientations over short regions.

Cross reactivity can be beneficial if an individual develops immunity to several related pathogens despite having been exposed to or vaccinated against only one of them. For instance, antibody cross reactivity may occur against the similar surface structures of various Gram-negative bacteria. Conversely, antibodies raised against pathogenic molecular components that resemble self molecules may incorrectly mark host cells for destruction, causing autoimmune damage. Patients who develop systemic lupus erythematosus (SLE) commonly exhibit antibodies that react with their own DNA. These antibodies may have been initially raised against the nucleic acid of microorganisms, but later cross-reacted with self-antigens. This phenomenon is also called molecular mimicry.

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SECTION OVERVIEW

11.7: Antibodies

Topic hierarchy

11.7A: Antibody Proteins and Antigen Binding

11.7B: Antibody Genes and Diversity

11.7C: Clonal Selection of Antibody-Producing Cells

11.7D: Isotype Class Switching

11.7E: Making Memory B Cells

11.7F: Primary and Secondary Antibody Responses

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11.7A: Antibody Proteins and Antigen Binding

A region at the tip of the antibody protein is very variable, allowing millions of antibodies with different antigen-binding sites to exist.

Learning Objectives

- Describe the general function and structure of an antibody

Key Points

- An antibody (Ab), also known as an immunoglobulin (Ig), is a large protein produced by B-cells that is used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses. The antibody recognizes a unique part of the foreign target, called an antigen.
- Each tip of the "Y" of an antibody contains a paratope that is specific for one particular epitope (analogous to a lock and key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can tag a microbe or an infected cell.
- The general structure of all antibodies is very similar: The Ig monomer is a Y-shaped molecule that consists of four polypeptide chains: two identical heavy chains and two identical light chains connected by disulphide bonds.
- Antibodies can occur in two physical forms, a soluble form that is secreted from the cell, and a membrane-bound form that is attached to the surface of a B-cell and is referred to as the B-cell receptor (BCR).

Key Terms

- **Hypervariable region**: In antibodies, hypervariable regions form the antigen-binding site and are found on both light and heavy chains. They also contribute to the specificity of each antibody. In a variable region, the 3 HV segments of each heavy or light chain fold together at the N-terminus to form an antigen binding pocket.

An antibody (Ab), also known as an immunoglobulin (Ig), is a large Y-shaped protein produced by B-cells that is used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses. The antibody recognizes a unique part of the foreign target, called an antigen. Each tip of the "Y" of an antibody contains a paratope (a structure analogous to a lock) that is specific for one particular epitope (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can tag a microbe, or an infected cell, for attack by other parts of the immune system, or can neutralize its target directly; for example, by blocking a part of a microbe that is essential for its invasion and survival. The production of antibodies is the main function of the humoral immune system.

Antibody Functions

Antibody functions include the following:

- Combine with viruses/toxins to prevent them from invading cells
- Attach to flagella of bacterium, restricting their movement
- Multi-bind to many bacteria at once, causing them to accumulate and prevent movement around the body
- Burst bacteria cell walls
- Attach to bacteria, making it easier for phagocytes to ingest them

Antibody Structure

Antibodies are heavy (~150 kDa) globular plasma proteins. They have sugar chains added to some of their amino acid residues; in other words, they are glycoproteins. Antibodies are typically made of the same basic structural units, each with two large heavy chains and two small light chains.

Heavy and light chains, variable and constant regions of an antibody

There are several different types of antibody heavy chains, and several different kinds of antibodies, which are grouped into different isotypes based on which heavy chain they possess. Five different antibody isotypes are known in mammals, which perform different roles, and help direct the appropriate immune response for each different type of foreign object they encounter.

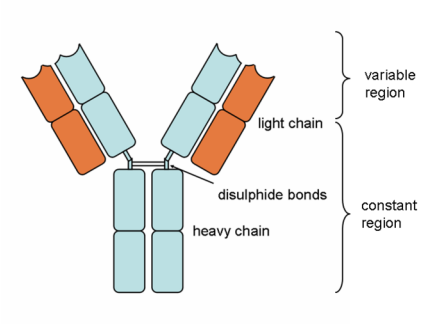

Figure: **Basic Antibody Structure**: Heavy and light chains, variable and constant regions of an antibody

The general structure of all antibodies is very similar. The Ig monomer is a Y-shaped molecule that consists of four polypeptide chains: two identical heavy chains, and two identical light chains connected by disulphide bonds. Each chain is composed of structural domains called immunoglobulin domains. These domains contain about 70-110 amino acids and are classified into different categories according to their size and function; for example, variable or IgV, and constant or IgC. The constant region determines the class of an immunoglobulin. All chains have a characteristic immunoglobulin fold in which two beta sheets create a "sandwich" shape, held together by interactions between conserved cysteines and other charged amino acids.

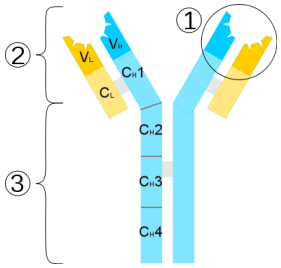

Figure: **Antigen Binding Fragment**: Scheme of an IgM/IgE with its costant (C) and variable (V) regions: 1) antigen binding fragment 2) Fab region 3) Fc regionblue: heavy chainsyellow: light chains

However, a small region at the tip of the protein is extremely variable, allowing millions of antibodies with slightly different tip structures, or antigen binding sites, to exist. This region is known as the hypervariable region. Each of these variants can bind to a different antigen. This enormous diversity of antibodies allows the immune system to recognize an equally wide variety of antigens. The large and diverse population of antibodies is generated by random combinations of a set of gene segments that encode different or paratopes, followed by random mutations in this area of the antibody gene, which create further diversity. The paratope is shaped at the amino terminal end of the antibody monomer by the variable domains from the heavy and light chains. The variable domain is also referred to as the FV region, and is the most important region for binding to antigens. More specifically, variable loops of β-strands, three each on the light (VL) and heavy (VH) chains are responsible for binding to the antigen.

Antibodies can occur in two physical forms, a soluble form that is secreted from the cell, and a membrane-bound form that is attached to the surface of a B cell and is referred to as the B cell receptor (BCR). The BCR is only found on the surface of B cells and facilitates the activation of these cells and their subsequent differentiation into either antibody factories called plasma cells, or memory B cells that will survive in the body and remember that same antigen so the B cells can respond faster upon future exposure. In most cases, interaction of the B cell with a T helper cell is necessary to produce full activation of the B cell and, therefore, antibody generation following antigen binding.

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11.7B: Antibody Genes and Diversity

Complex genetic mechanisms evolved which allow vertebrate B cells to generate a diverse pool of antibodies from relatively few antibody genes.

Learning Objectives

- Outline the two stages which result in antibody diversity: somatic (V(D)J) and recombination stages

Key Points

- Virtually all microbes can trigger an antibody response. Successful recognition and eradication of many different types of microbes requires diversity among antibodies, a result of variation in amino acid composition that allows them to interact with many different antigens.
- Antibodies obtain their diversity through 2 processes. The first is called V(D)J (variable, diverse, and joining regions) recombination. During cell maturation, the B cell splices out the DNA of all but one of the genes from each region and combine the three remaining genes to form one VDJ segment.
- The second stage of recombination occurs after the B cell is activated by an antigen.In these rapidly dividing cells, the genes encoding the variable domains of the heavy and light chains undergo a high rate of point mutation, by a process called somatic hypermutation.
- As a consequence of these processes any daughter B cells will acquire slight amino acid differences in the variable domains of their antibody chains.This serves to increase the diversity of the antibody pool and impacts the antibody's antigen-binding affinity.
- Point mutations can result in the production of antibodies that have a lower or higher affinity with their antigen than the original antibody. B cells expressing antibodies with a higher affinity for the antigen will outcompete those with weaker affinities (called affinity maturation).

Key Terms

- **Somatic hypermutation**: a cellular mechanism by which the immune system adapts to the new foreign elements that confront it (for example, microbes). A major component of the process of affinity maturation, SHM diversifies B cell receptors used to recognize foreign elements (antigens) and allows the immune system to adapt its response to new threats during the lifetime of an organism.
- **V(D)J recombination**: Also known as somatic recombination, this is a mechanism of genetic recombination in the early stages of immunoglobulin (Ig) and T cell receptors (TCR) production of the immune system.

Virtually all microbes can trigger an antibody response. Successful recognition and eradication of many different types of microbes requires diversity among antibodies (glycoproteins belonging to the immunoglobulin superfamily). It is the variety in their amino acid composition that allows them to interact with many different antigens. It has been estimated that humans generate about 10 billion different antibodies, each capable of binding a distinct epitope of an antigen. Although a huge repertoire of different antibodies is generated in a single individual, the number of genes available to make these proteins is limited by the size of the human genome. Several complex genetic mechanisms have evolved that allow vertebrate B cells to generate a diverse pool of antibodies from a relatively small number of antibody genes.

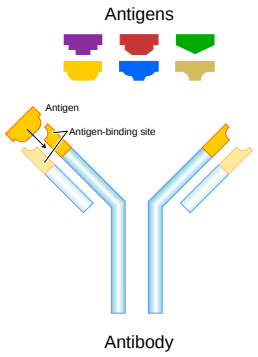

Figure: **Antibodies bind to specific antigens**: Schematic diagram of an antibody and antigens. Light chains are in lighter blue and orange, heavy chains in darker blue and orange. Each antibody binds to a specific antigen; an interaction similar to a lock and key.

Antibody Structure

Antibodies are typically made of basic structural units—each with two large heavy chains and two small light chains. There are several different types of antibody heavy chains, and several different kinds of antibodies, which are grouped into different isotypes based on which heavy chain they possess. Five different antibody isotypes are known in mammals, which perform different roles, and help direct the appropriate immune response for each different type of foreign object they encounter. Though the general structure of all antibodies is very similar, a small region at the tip of the protein is extremely variable, allowing millions of antibodies with slightly different antigen binding sites to exist. This region is known as the hypervariable region. Each of these variants can bind to a different antigen. This enormous diversity of antibodies allows the immune system to recognize an equally wide variety of antigens.

Antibodies obtain their diversity through two processes:

V(D)J Recombination

The first stage is called somatic, or V(D)J, which stands for variable, diverse, and joining regions recombination. Several sets of genes are located within each of the three regions. During cell maturation, the B cell will splice out the DNA of all but one of the genes from each region and combine the three remaining genes together to form one VDJ segment. This segment, along with a constant region gene, forms the basis for subsequent antibody production.

It is estimated that given the number of variants in each of the three regions, approximately 10,000-20,000 unique antibodies are producible. V(D)J recombination takes place in the primary lymphoid tissue (bone marrow for B cells, and thymus for T cells) and nearly randomly combines variable, diverse, and joining gene segments. It is due to this randomness in choosing different genes that it is able to diversely encode proteins to match antigens.

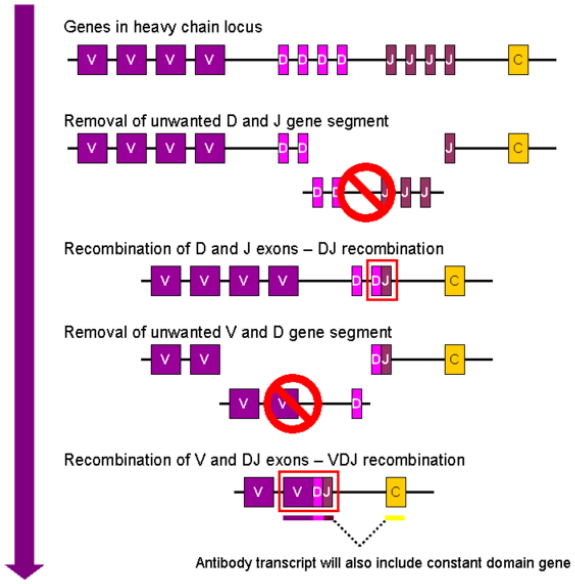

Figure: **Redistribution within the immunoglobulin (antibody) gene**: Schematic overview of V(D)J recombination.

Somatic Hypermutation

The second stage of recombination occurs after the B cell is activated by an antigen. In these rapidly dividing cells, the genes encoding the variable domains of the heavy and light chains undergo a high rate of point mutation, by a process called somatic hypermutation (SHM). SHM is a cellular mechanism by which the immune system adapts to the new foreign elements that confront it and is a major component of the process of affinity maturation. SHM diversifies B cell receptors used to recognize antigens and allows the immune system to adapt its response to new threats during the lifetime of an organism. Somatic hypermutation involves a programmed process of mutation affecting the variable regions of immunoglobulin genes. SHM results in approximately one nucleotide change per variable gene, per cell division. As a consequence, any daughter B cells will acquire slight amino acid differences in the variable domains of their antibody chains. This serves to increase the diversity of the antibody pool and impacts the antibody's antigen-binding affinity. Some point mutations will result in the production of antibodies that have a lower affinity

with their antigen than the original antibody, and some mutations will generate antibodies with a higher affinity. B cells that express higher affinity antibodies on their surface will receive a strong survival signal during interactions with other cells, whereas those with lower affinity antibodies will not, and will die by apoptosis. Thus, B cells expressing antibodies with a higher affinity for the antigen will outcompete those with weaker affinities for function and survival. The process of generating antibodies with increased binding affinities is called affinity maturation. Affinity maturation occurs after V(D)J recombination, and is dependent on help from helper T cells.

Antibody genes also re-organize in a process called class switching, which changes the base of the heavy chain to another. This creates a different isotype of the antibody while retaining the antigen specific variable region, thus allowing a single antibody to be used by several different parts of the immune system.

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11.7C: Clonal Selection of Antibody-Producing Cells

The clonal selection hypothesis is a widely accepted model for the immune system's response to infection.

Learning Objectives

- Describe the clonal selection hypothesis in regards to the production of B cells

Key Points

- In 1954, immunologist Niels Jerne put forth the hypothesis that there is already a vast array of lymphocytes in the body before infection. The entrance of an antigen into the body results in the selection of only one type of lymphocyte to match it and produce a corresponding antibody to destroy it.
- B cells exist as clones derived from a particular cell. Thus the antibodies and their differentiated progenies can recognize and/or bind the same specific surface components composed of biological macromolecules of a given antigen. Clonality has important consequences for immunogenic memory.
- The clonal selection hypothesis states that an individual B cell expresses receptors specific to the distinct antigen, determined before the antibody ever encounters the antigen.

Key Terms

- **clonal selection**: An hypothesis which states that an individual lymphocyte (specifically, a B cell) expresses receptors specific to the distinct antigen, determined before the antibody ever encounters the antigen. Binding of Ag to a cell activates the cell, causing a proliferation of clone daughter cells.
- **clone**: A group of identical cells derived from a single cell.

The clonal selection hypothesis has become a widely accepted model for how the immune system responds to infection and how certain types of B and T lymphocytes are selected for destruction of specific antigens invading the body.

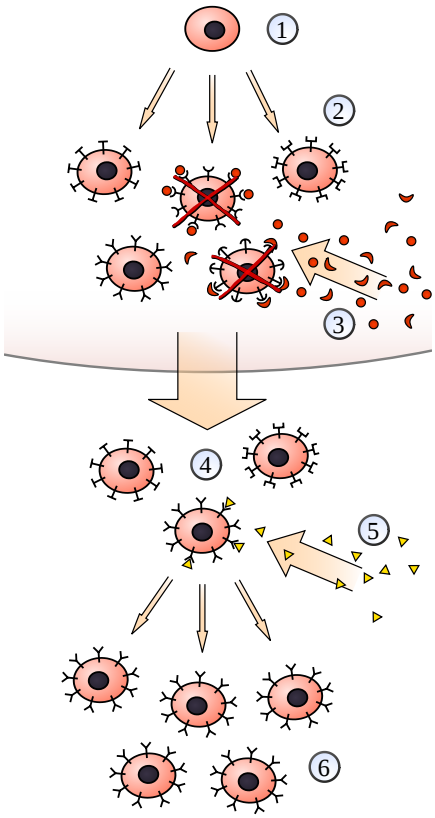

Figure: **A schematic view of clonal selection**: Clonal selection of lymphocytes: 1) A hematopoietic stem cell undergoes differentiation and genetic rearrangement to produce 2) immature lymphocytes with many different antigen receptors. Those that bind to 3) antigens from the body's own tissues are destroyed, while the rest mature into 4) inactive lymphocytes. Most of these will never encounter a matching 5) foreign antigen, but those that do are activated and produce 6) many clones of themselves.

Four predictions of the clonal selection hypothesis

- Each lymphocyte bears a single type of receptor with a unique specificity (by V(D)J recombination).
- Receptor occupation is required for cell activation.
- The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity as the parental cell.
- Those lymphocytes bearing receptors for self molecules will be deleted at an early stage.

In 1954, Danish immunologist Niels Jerne put forward a hypothesis which stated that there is already a vast array of lymphocytes in the body prior to any infection. The entrance of an antigen into the body results in the selection of only one type of lymphocyte to match it and produce a corresponding antibody to destroy the antigen. This selection of only one type of lymphocyte results in it being cloned or reproduced by the body extensively to ensure there are enough antibodies produced to inhibit and prevent infection. Australian immunologist Frank Macfarlane Burnet, with input from David W. Talmage, worked on this model and was the first to name it "clonal selection theory. " Burnet explained immunological memory as the cloning of two types of lymphocyte. One clone acts immediately to combat infection whilst the other is longer lasting, remaining in the immune system for a long time, which results in immunity to that antigen. In 1958, Sir Gustav Nossal and Joshua Lederberg showed that one B cell always produces only one antibody, which was the first evidence for clonal selection theory.

B cells exist as clones. All B cells derive from a particular cell, and as such, the antibodies and their differentiated progenies can recognize and/or bind the same specific surface components composed of biological macromolecules (epitope) of a given antigen. Such clonality has important consequences, as immunogenic memory relies on it. The great diversity in immune response comes about due to the up to 109 clones with specificities for recognizing different antigens. Upon encountering its specific antigen, a single B cell, or a clone of cells with shared specificity, divides to produce many B cells. Most of such B cells differentiate into

plasma cells that secrete antibodies into blood that bind the same epitope that elicited proliferation in the first place. A small minority survives as memory cells that can recognize only the same epitope. However, with each cycle, the number of surviving memory cells increases. The increase is accompanied by affinity maturation which induces the survival of B cells that bind to the particular antigen with high affinity. This subsequent amplification with improved specificity of immune response is known as secondary immune response. B cells that have not been activated by antigen are known as naive lymphocytes; those that have met their antigen, become activated, and have differentiated further into fully functional lymphocytes are known as effector B lymphocytes.

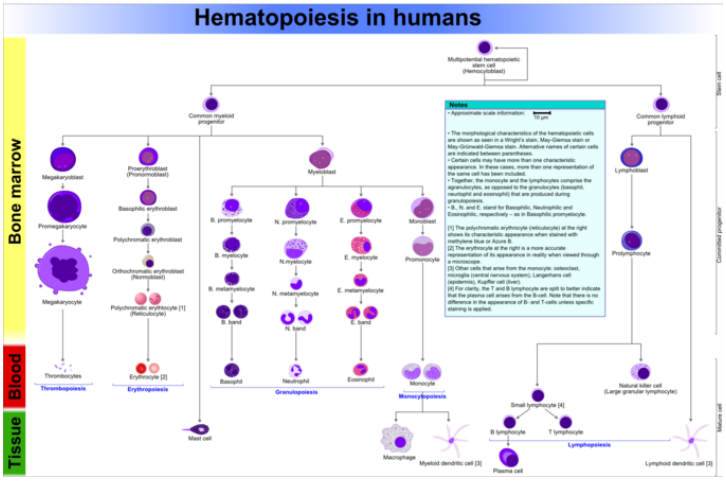

Figure: **Hematopoiesis in Humans**: This diagram shows hematopoiesis as it occurs in humans.

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11.7D: Isotype Class Switching

Isotype class switching is a biological mechanism that changes a B cell's production of antibody from one class to another.

Learning Objectives

- Describe the process of class switch recombination that results in changes in the antibody-heavy chain

Key Points

- The antibody isotype of a B cell changes during cell development and activation. Immature B cells have never been exposed to an antigen and are known as naïve B cells. B cells begin to express both IgM and IgD when they reach maturity and renders the B cell 'mature' and ready to respond to antigen.
- If activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies that have defined roles in the immune system.
- During class switch recombination the constant region portion of the antibody-heavy chain is changed, but the variable region of the heavy chain stays the same; thus, class switching does not affect antigen specificity.
- The antibody retains affinity for the same antigens, but can interact with different effector molecules. This allows different daughter cells from the same activated B cell to produce antibodies of different isotypes or subtypes (e.g. IgG1, IgG2 etc.).

Key Terms

- **isotype**: Antibodies can come in different varieties known as isotypes, which refer to the genetic variations or differences in the constant regions of the heavy and light chains of the antibody.
- **class switch recombination**: A biological mechanism that changes a B cell's production of antibody from one class to another; for example, from an isotype called IgM to an isotype called IgG.

Isotype Class Switching

Antibodies can come in different varieties, known as isotypes or classes. In placental mammals there are five antibody isotypes: IgA, IgD, IgE, IgG and IgM. They are each named with an "Ig" prefix that stands for immunoglobulin (another name for antibody) and differ in their biological properties, functional locations, and ability to deal with different antigens.

The antibody isotype of a B cell changes during cell development and activation. Immature B cells, which have never been exposed to an antigen, are known as naïve B cells and express only the IgM isotype in a cell surface bound form. B cells begin to express both IgM and IgD when they reach maturity; the co-expression of both of these immunoglobulin isotypes renders the B cell 'mature' and ready to respond to an antigen. B cell activation follows engagement of the cell-bound antibody molecule with an antigen, causing the cell to divide and differentiate into an antibody-producing cell, called a plasma cell. In this activated form, the B cell starts to produce antibody in a secreted form rather than a membrane-bound form. If these activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies (from IgM or IgD) that have defined roles in the immune system.

Immunoglobulin class switching (or isotype switching, or isotypic commutation, or class switch recombination (CSR)) is a biological mechanism that changes a B cell's production of antibody from one class to another; for example, from an isotype called IgM to an isotype called IgG. During this process, the constant region portion of the antibody-heavy chain is changed, but the variable region of the heavy chain stays the same (the terms "constant" and "variable" refer to changes or lack thereof between antibodies that target different epitopes). Since the variable region does not change, class switching does not affect antigen specificity. Instead, the antibody retains affinity for the same antigens, but can interact with different effector molecules. This allows different daughter cells from the same activated B cell to produce antibodies of different isotypes or subtypes (e.g. IgG1, IgG2 etc.).

Class switching occurs by a mechanism called class switch recombination (CSR) binding. Class switch recombination is a biological mechanism that allows the class of antibody produced by an activated B cell to change during a process known as isotype or class switching. During CSR, portions of the antibody-heavy chain locus are removed from the chromosome, and the gene segments surrounding the deleted portion are rejoined to retain a functional antibody gene that produces antibody of a different isotype. Double-stranded breaks are generated in DNA at conserved nucleotide motifs, called switch (S) regions, which

are upstream from gene segments that encode the constant regions of antibody-heavy chains; these occur adjacent to all heavy chain constant region genes with the exception of the δ-chain. DNA is nicked and broken at two selected S-regions by the activity of a series of enzymes, including Activation-Induced (Cytidine) Deaminase (AID), uracil DNA glycosylase and apyrimidic/apurinic (AP)-endonucleases. The intervening DNA between the S-regions is subsequently deleted from the chromosome, removing unwanted μ or δ heavy chain constant region exons and allowing substitution of a γ, α or ε constant region gene segment. The free ends of the DNA are rejoined by a process called non-homologous end joining (NHEJ) to link the variable domain exon to the desired downstream constant domain exon of the antibody-heavy chain. In the absence of non-homologous end joining, free ends of DNA may be rejoined by an alternative pathway biased toward microhomology joins. With the exception of the μ and δ genes, only one antibody class is expressed by a B cell at any point in time.

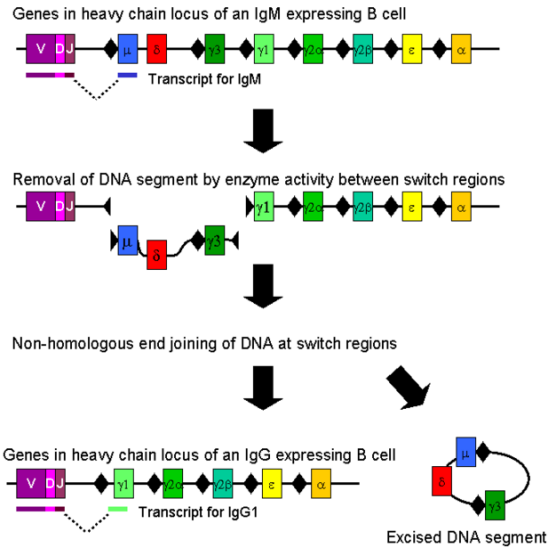

Figure: **Class Switch Recombination**: Mechanism of class switch recombination that allows isotype switching in activated B cells.

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11.7E: Making Memory B Cells

Memory B cells are a B cell sub-type that are formed following primary infection.

Learning Objectives

- Outline the process of memory B cell production

Key Points

- In the wake of the first (primary response) infection involving a particular antigen, the responding naïve cells (ones which have never been exposed to the antigen) proliferate to produce a colony of cells, most of which differentiate into the plasma cells, also called effector B cells.
- Effector B cells (which produce the antibodies) clear away with the resolution of infection, and the rest persist as the memory cells that can survive for years, or even a lifetime.
- The antibody molecules present on a clone (a group of genetically identical cells) of B cells have a unique paratope. Some of the resulting paratopes (and the cells elaborating them) have a better affinity for the antigen and are more likely to proliferate than the others.

Key Terms

- **paratope**: That part of the molecule of an antibody that binds to an antigen
- **memory cell**: one of a number of types of white blood cells

Making Memory B Cells

Memory B cells are a B cell sub-type that are formed following a primary infection. In the wake of the first (primary response) infection involving a particular antigen, the responding naïve cells (ones which have never been exposed to the antigen) proliferate to produce a colony of cells. Most of them differentiate into the plasma cells, also called effector B cells (which produce the antibodies) and clear away with the resolution of infection. The rest persist as the memory cells that can survive for years, or even a lifetime.

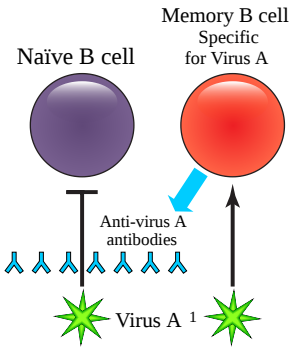

Figure: **B memory cells**: B lymphocytes are the cells of the immune system that make antibodies to invading pathogens like viruses. They form memory cells that remember the same pathogen for faster antibody production in future infections. The body's immune system has a propensity to preferentially utilize immunological memory based on a previous infection when a second slightly different version of that foreign entity is encountered.

To understand the events taking place, it is important to appreciate that the antibody molecules present on a clone (a group of genetically identical cells) of B cells have a unique paratope (the sequence of amino acids that binds to the epitope on an antigen).

Each time these cells are induced to proliferate due to an infection, the genetic region coding for the paratope undergoes spontaneous mutations with a frequency of about 1 in every 1600 cell divisions. This may not seem high, but because the cells divide so often, it ends up resulting in many mutations. The frequency of mutations in other cells is around 1 in 10^6, which is much lower.

All these events occur in the highly "eventful" germinal centers of lymphoid follicles, within the lymph nodes.

Some of the resulting paratopes (and the cells elaborating them) have a better affinity for the antigen (actually, the epitope) and are more likely to proliferate than the others.

Moreover, the number of different clones responding to the same antigen increases (polyclonal response) with each such exposure to the antigen and a greater number of memory cells persist. Thus, a stronger (basically, larger number of antibody molecules) and more specific antibody production is the hallmark of secondary antibody response.

The fact that all the cells of a single clone elaborate one (and only one) paratope, and that the memory cells survive for long periods, is what imparts a memory to the immune response. This is the principle behind vaccination and administration of booster.

The paratope is the part of an antibody which recognizes an antigen, the antigen-binding site of an antibody. It is a small region (15–22 amino acids) of the antibody's Fv region and contains parts of the antibody's heavy and light chains. The part of the antigen to which the paratope binds is called an epitope.

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11.7F: Primary and Secondary Antibody Responses

The immune system protects organisms from infection first with the innate immune system, then with adaptive immunity.

Learning Objectives

- Generalize the role of the innate and adaptive immune system in regards to antibody response

Key Points

- When B cells and T cells are first activated by a pathogen, memory B-cells and T- cells develop.
- Throughout the lifetime of an animal these memory cells will “remember” each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again. This type of immunity is both active and adaptive.
- Active immunity often involves both the cell-mediated and humoral aspects of immunity as well as input from the innate immune system.

Key Terms

- **secondary response**: the immune response occurring on second and subsequent exposures to an antigen, with a stronger response to a lesser amount of antigen, and a shorter lag time compared to the primary immune response
- **primary response**: the immune response occurring on the first exposure to an antigen, with specific antibodies appearing in the blood after a multiple day latent period
- **adaptive immunity**: the components of the immune system that adapt themselves to each new disease encountered and are able to generate pathogen-specific immunity.

The immune system is a system of biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, from viruses to parasitic worms, and distinguish them from the organism’s own healthy tissue. Pathogens can rapidly evolve and adapt to avoid detection and neutralization by the immune system. As a result, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. Even simple unicellular organisms such as bacteria possess a rudimentary immune system, in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants and insects. These mechanisms include phagocytosis, antimicrobial peptides called defensins, and the complement system. Jawed vertebrates, including humans, have even more sophisticated defense mechanisms, including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive (or acquired) immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

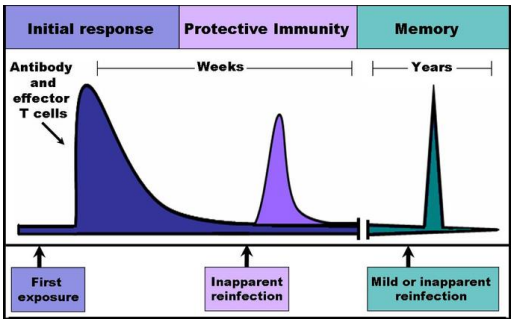

Figure: **The Time Course of an Immune Response**: Immune reactants, such as antibodies and effector T-cells, work to eliminate an infection, and their levels and activity rapidly increase following an encounter with an infectious agent, whether that agent is a pathogen or a vaccine. For several weeks these reactants remain in the serum and lymphatic tissues and provide protective immunity against reinfection by the same agent. During an early reinfection, few outward symptoms of illness are present, but the levels of immune reactants increase and are detectable in the blood and/or lymph. Following clearance of the infection, antibody level and effector T cell activity gradually declines. Because immunological memory has developed, reinfection at later times leads to a rapid increase in antibody production and effector T cell activity. These later infections can be mild or even inapparent.

Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer. Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. In humans, immunodeficiency can either be the result of a genetic disease such as severe combined immunodeficiency, acquired conditions such as HIV/AIDS, or the use of immunosuppressive medication. In contrast, autoimmunity results from a hyperactive immune

system attacking normal tissues as if they were foreign organisms. Common autoimmune diseases include Hashimoto's thyroiditis, rheumatoid arthritis, diabetes mellitus type 1, and systemic lupus erythematosus. Immunology covers the study of all aspects of the immune system.

The immune system protects organisms from infection with layered defenses of increasing specificity. In simple terms, physical barriers prevent pathogens such as bacteria and viruses from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system, which is activated by the innate response. Here, the immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the adaptive immune system to mount faster and stronger attacks each time this pathogen is encountered. Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non-self molecules. In immunology, self molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system. Conversely, non-self molecules are those recognized as foreign molecules. One class of non-self molecules are called antigens (short for antibody generators) and are defined as substances that bind to specific immune receptors and elicit an immune response.

When B cells and T cells are first activated by a pathogen, memory B-cells and T- cells develop. Throughout the lifetime of an animal these memory cells will "remember" each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again. This type of immunity is both *active* and *adaptive* because the body's immune system prepares itself for future challenges. Active immunity often involves both the cell-mediated and humoral aspects of immunity as well as input from the innate immune system. The *innate system* is present from birth and protects an individual from pathogens regardless of experiences, whereas adaptive immunity arises only after an infection or immunization and hence is "acquired" during life.

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11.8: T Cells and Cellular Immunity

Topic hierarchy

11.8A: Cytotoxic T Lymphocytes and Mucosal Surfaces

11.8B: Classes of T Cells

11.8C: Cell-Mediated Immunity

11.8D: Regulatory T Cells

11.8E: T Cell Receptors

11.8F: Adaptive Immunity and the Immunoglobulin Superfamily

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11.8A: Cytotoxic T Lymphocytes and Mucosal Surfaces

The lymphatic system houses large populations of immune cells which are released upon detection of a pathogen.

Learning Objectives

- Describe the features of the lymphatic system as they relate to the immune response

Key Points

- The lymphatic system contains lymph: a fluid that bathes tissues and organs and contains white blood cells (not red blood cells).
- Once B and T cells mature, the majority of them enter the lymphatic system, where they are stored in lymph nodes until needed.
- Lymph nodes also store dendritic cells and macrophages; as antigens are filtered through the lymphatic system, these cells collect them so as to present them to B and T cells.
- The spleen, which is to blood what lymph nodes are to lymph, filters foreign substances and antibody -complexed pathogens from the blood.

Key Terms

- **lymph**: a colorless, watery, bodily fluid carried by the lymphatic system, consisting mainly of white blood cells

Lymphatic system

Lymph, the watery fluid that bathes tissues and organs, contains protective white blood cells, but does not contain erythrocytes (red blood cells). Lymph moves about the body through the lymphatic system, which is made up of vessels, lymph ducts, lymph glands, and organs such as tonsils, adenoids, thymus, and spleen. Although the immune system is characterized by circulating cells throughout the body, the regulation, maturation, and intercommunication of immune factors occur at specific sites that are known as lymph nodes.

The blood circulates immune cells, proteins, and other factors through the body. Approximately 0.1 percent of all cells in the blood are leukocytes, which include monocytes (the precursor of macrophages) and lymphocytes. Most cells in the blood are red blood cells. Cells of the immune system can travel between the distinct lymphatic and blood circulatory systems, which are separated by interstitial space, by a process called extravasation (passing through to surrounding tissue).

Recall that cells of the immune system originate from stem cells in the bone marrow. B cell maturation occurs in the bone marrow, whereas progenitor cells migrate from the bone marrow and develop and mature into naïve T cells in the organ called the thymus. On maturation, T and B lymphocytes circulate to various destinations. Lymph nodes scattered throughout the body house large populations of T and B cells, dendritic cells, and macrophages. Lymph gathers antigens as it drains from tissues. These antigens are filtered through lymph nodes before the lymph is returned to circulation. Antigen-presenting cells (APCs) in the lymph nodes capture and process antigens, informing nearby lymphocytes about potential pathogens.

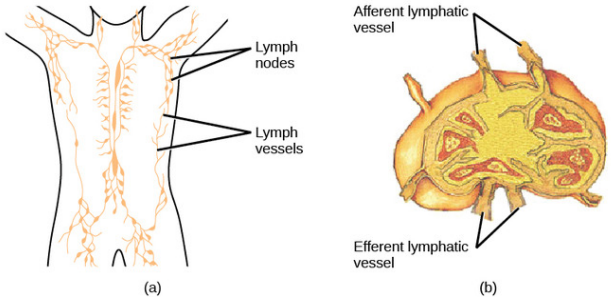

Figure: **Lymphatic system**: (a) Lymphatic vessels carry a clear fluid called lymph throughout the body. The liquid passes through (b) lymph nodes that filter the lymph that enters the node through afferent vessels, leaving through efferent vessels. Lymph nodes are filled with lymphocytes that purge infecting cells.

The spleen houses B and T cells, macrophages, dendritic cells, and NK cells. The spleen is also the site where APCs that have trapped foreign particles in the blood can communicate with lymphocytes. Antibodies are synthesized and secreted by activated plasma cells in the spleen, which filters foreign substances and antibody-complexed pathogens from the blood. Functionally, the spleen is to the blood as lymph nodes are to the lymph.

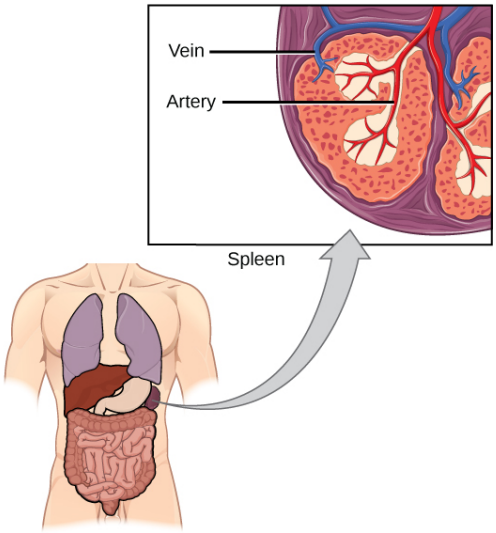

Figure: **Spleen in the lymphatic system**: The spleen functions to immunologically filter the blood and allow for communication between cells corresponding to the innate and adaptive immune responses.

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11.8B: Classes of T Cells

T cells play a central role in cell-mediated immune response through the use of the surface T cell receptor to recognize peptide antigens.

Learning Objectives

- Distinguish between: naive, effector (helper and cytotoxic), memory and regulatory T cells

Key Points

- T cell progenitors are derived from the bone marrow but travel to the thymus where they mature.
- T cells can be divided into three main subtypes: effector, memory, and regulatory cells. Each type performs a distinct function during an immune response to foreign antigens.
- T cells subtypes are differentiated by the expression of unique cell surface markers, such as CD4 for helper T cells and CD8 for cytolytic or cytotoxic T cells.

Key Terms

- **cytotoxic**: of, relating to, or being a cytotoxin
- **cytolytic**: Of or pertaining to cytolysis

Cellular immunity is mediated by *T lymphocytes*, also called T cells. Their name refers to the organ from which they're produced: the thymus. This type of immunity promotes the destruction of microbes residing in phagocytes, or the killing of infected cells to eliminate reservoirs of infection. T cells do not produce antibody molecules. They have antigen receptors that are structurally related to antibodies. These structures help recognize antigens only in the form of peptides displayed on the surface of antigen-presenting cells.

T cells consist of functionally distinct populations. These include naive T cells that recognize antigens and are activated in peripheral lymphoid organs. This activation results in the expansion of the antigen-specific lymphocyte pool and the differentiation of these cells into effector and memory cells. Effector cells include helper T cells, and cytolytic or cytotoxic T cells. In response to antigenic stimulation, helper T cells (characterized by the expression of CD4 marker on their surface) secrete proteins called cytokines, whose function is to stimulate the proliferation and differentiation of the T cells themselves, as well as other cells, including B cells, macrophages, and other leukocytes. Cytolytic or cytotoxic T cells (characterized by the expression of CD8 marker on their surface) kill cells that produce foreign antigens, such as cells infected by viruses and other intracellular microbes.

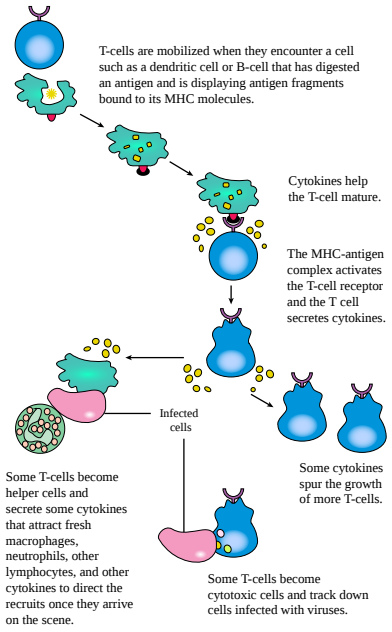

Figure: **Cell-mediated immunity**: T cells promote the killing of cells that have ingested microorganisms and present foreign antigens on their surface.

Memory T cells are an expanded population of T cells specific for antigens that can respond rapidly to subsequent encounter with that antigen and differentiate into effector cell to eliminate the antigen. Another class of T cells called regulatory T cells function to inhibit immune response and resolve inflammation. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction.

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11.8C: Cell-Mediated Immunity

Cell-mediated immunity involves cytotoxic T cells recognizing infected cells and bringing about their destruction.

Learning Objectives

- Summarize the cell-mediated immune response

Key Points

- Once a pathogen enters a cell, it can no longer be detected by the humoral immune response; instead, the cell-mediated immune response must take over to kill the infected cell before it can allow the virus or bacteria to replicate and spread.
- T cells recognize infected cells by interacting with antigen present on their MHC II molecules; before a T cell can do so, it must be activated via interaction with an antigen presenting cell, or APC.
- Once a cytotoxic T cell (T_C) is activated, it will clone itself, producing many T_C cells with the correct receptors; some portion of the cells are active and will help destroy infected cells, while others are inactive memory cells that will create more active T_C cells if the infection returns.
- Helper T cells (T_H cells) also aid in cell-mediated immunity by releasing signaling molecules known as cytokines which can recruit natural killer cells and phagocytes to destroy infected cells and further activate T_C cells; they do not directly destroy pathogens.

Key Terms

- **cytotoxic T cell**: a subgroup of lymphocytes (white blood cells) that are capable of inducing death to infected somatic or tumor cells; part of cell-mediated immunity
- **cytokine**: any of various small regulatory proteins that regulate the cells of the immune system; they are released upon binding of PRRs to PAMPS

T cells

Just as the humoral immune response has B cells which mediate its response, the cellular immune response has T cells, which recognize infected cells and destroy them before the pathogen inside can replicate and spread to infect other cells. Unlike B cells, T lymphocytes (T cells) are unable to recognize pathogens without assistance. First, an antigen-presenting cell (APC, such as a dendritic cell or a macrophage) detects, engulfs (via phagocytosis in the case of macrophages or by entry of the pathogen of its own accord in the case of dendritic cells), and digests pathogens into hundreds or thousands of antigen fragments. These fragments are then transported to the surface of the APC, where they are presented on proteins known as Major Histocompatibility Complexes class II (MHC II, see). T cells become activated towards a certain antigen once they encounter it displayed on an MHC II. After a virus or bacteria enters a cell, it can no longer be detected by the humoral immune response. Instead, the cellular immune response must take over. To do so, a T cell will become activated by interacting with an antigen of the infecting cell or virus presented on the MHC II of an APC.

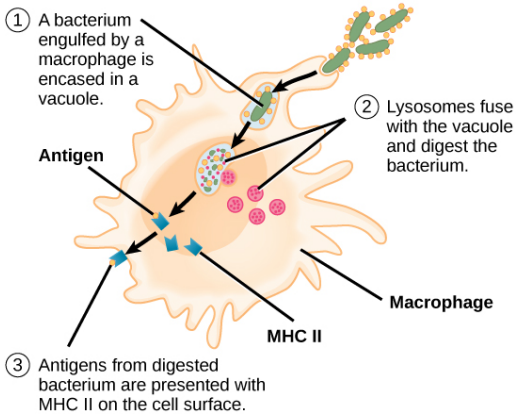

Figure: **APCs, MHCs and lymphocytes**: An antigen-presenting cell (APC), such as a macrophage, engulfs a foreign antigen, partially digests it in a lysosome, and then embeds it in an MHC class II molecule for presentation at the cell surface. Lymphocytes of the adaptive immune response must interact with antigen-embedded MHC class II molecules to mature into functional immune cells.

Cytotoxic T cells mediate one arm of the cellular immune response

There are two main types of T cells: helper T lymphocytes (T_H) and the cytotoxic T lymphocytes (T_C). The T_H lymphocytes function indirectly to tell other immune cells about potential pathogens, while cytotoxic T cells (T_C) are the key component of the cell-mediated part of the adaptive immune system which attacks and destroys infected cells. $T_C$cells are particularly important in protecting against viral infections because viruses replicate within cells where they are shielded from extracellular contact with circulating antibodies. Once activated, the $T_C$creates a large clone of cells with one specific set of cell-surface receptors, similar to the proliferation of activated B cells. As with B cells, the clone includes active T_C cells and inactive memory T_C cells. The resulting active T_C cells then identify infected host cells.

T_C cells attempt to identify and destroy infected cells by triggering apoptosis (programmed cell death) before the pathogen can replicate and escape, thereby halting the progression of intracellular infections. To recognize which cells to pursue, T_C recognize antigens presented on MHC I complexes, which are present on all nucleated cells. MHC I complexes display a current readout of intracellular proteins inside a cell and will present pathogen antigens if the pathogen is present in the cell. T_C cells also support NK lymphocytes to destroy early cancers.

Cytokines released by T_H cells recruit NK cells and phagocytes

Cytokines are signaling molecules secreted by a T_H cell in response to a pathogen-infected cell; they stimulate natural killer cells and phagocytes such as macrophages. Phagocytes will then engulf infected cells and destroy them. Cytokines are also involved in stimulating T_C cells, enhancing their ability to identify and destroy infected cells and tumors. A summary of how the humoral and cell-mediated immune responses are activated appears in. B plasma cells and T_C cells are collectively called effector cells because they are involved in “effecting” (bringing about) the immune response of killing pathogens and infected host cells.

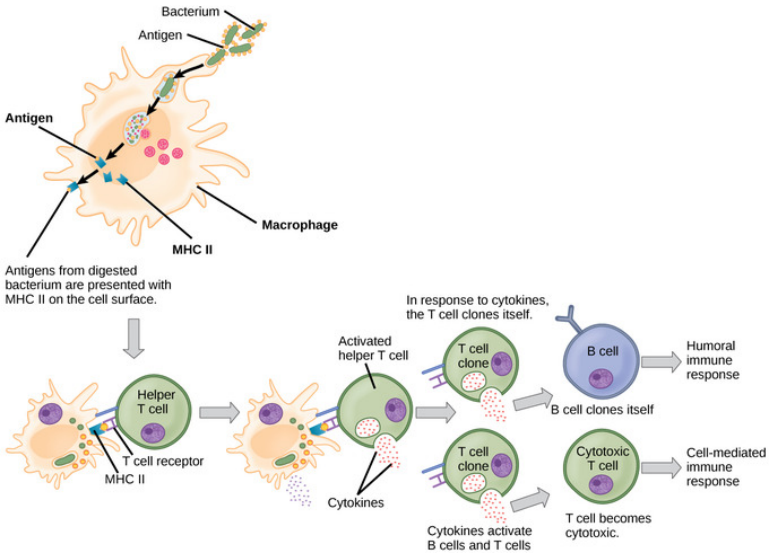

Figure: **Helper T cells in the immune response**: A helper T cell becomes activated by binding to an antigen presented by an APC via the MHCII receptor, causing it to release cytokines. Depending on the cytokines released, this activates either the humoral or the cell-mediated immune response.

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11.8D: Regulatory T Cells

Regulatory T cells are a subset of T cells which modulate the immune system and keep immune reactions in check.

Learning Objectives

- Describe the function and types of regulatory T cells

Key Points

- Regulatory T cells (Tregs) are critical to the maintenance of immune cell homeostasis as evidenced by the consequences of genetic or physical ablation of the Treg population.
- Tregs are classified into natural or induced Tregs; natural Tregs are CD4+CD25+ T-cells which develop, and emigrate from the thymus to perform their key role in immune homeostasis.
- Adaptive Tregs are non-regulatory CD4+ T-cells which acquire CD25 (IL-2R alpha) expression outside of the thymus and are typically induced by inflammation and disease processes, such as autoimmunity and cancer.

Key Terms

- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.

Regulatory T cells are a component of the immune system that suppress immune responses of other cells. This is an important "self-check" built into the immune system to prevent excessive reactions and chronic inflammation. Regulatory T cells come in many forms, with the most well-understood being those that express CD4, CD25, and Foxp3. These cells are also called $CD4^+CD25^+$ regulatory T cells, or Tregs. These cells are involved in shutting down immune responses after they have successfully eliminated invading organisms, and also in preventing autoimmunity.

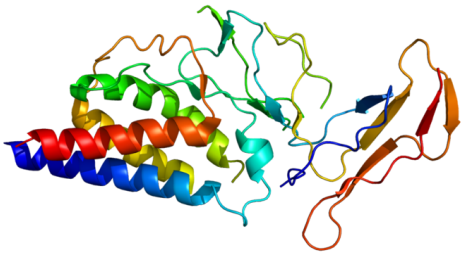

Figure: **CD25 is a component of the IL2 receptor**: Interleukin 2 receptor is composed of three subunits (alpha, beta, and gamma). CD25 constitutes the alpha chain of the IL2 receptor.

$CD4^+Foxp3^+$ regulatory T cells have been called "naturally-occurring" regulatory T cells, to distinguish them from "suppressor" T cell populations that are generated *in vitro*. Additional suppressor T cell populations include Tr1, Th3, $CD8^+CD28^-$, and Qa-1 restricted T cells. The contribution of these populations to self- tolerance and immune homeostasis is less well defined. FOXP3 can be used as a good marker for CD4+CD25+ T cells as well as recent studies showing evidence for FOXP3 in CD4+CD25- T cells.

An additional regulatory T cell subset, induced regulatory T cells, are also needed for tolerance and suppression. Induced Regulatory T (iTreg) cells ($CD4^+CD25^+Foxp3^+$) are suppressive cells involved in tolerance. iTreg cells have been shown to suppress T cell proliferation and experimental autoimmune diseases. iTreg cells develop from mature $CD4^+$ conventional T cells outside of the thymus: a defining distinction between natural regulatory T (nTreg) cells and iTreg cells. Though iTreg and nTreg cells share a similar function iTreg cells have recently been shown to be an essential non-redundant regulatory subset that supplements nTreg cells, in part by expanding TCR diversity within regulatory responses. Acute depletion of the iTreg cell pool in mouse models has resulted in inflammation and weight loss. The contribution of nTreg cells versus iTreg cells in maintaining tolerance is unknown, but both are important. Epigenetic differences have been observed between nTreg and iTreg cells, with the former having more stable Foxp3 expression and wider demethylation.

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11.8E: T Cell Receptors

Learning Objectives

- Discuss the role of the T cell receptor (TCR)

T lymphocytes have a dual specificity: they recognize polymorphic residues of self major histocompatibility complex (MHC) molecules, which accounts for their MHC restriction; they also recognize residues of peptide antigens displayed by these MHC molecules, which is responsible for their specificity. MHC molecules and peptides form complexes on the surface of antigen presenting cells (APCs). The receptor that recognizes these peptide-MHC complexes is called the T Cell Receptor (TCR). Clones of T cells with different specificities express different TCRs.

The biochemical signals that are triggered in T cells following antigen recognition are transduced not by the TCR itself, but by invariant proteins (CD3, and zeta), which are non-covalently linked to the antigen receptor to form the TCR complex. T cells also express other membrane receptors that do not recognize antigens but participate in responses to antigens; these are collectively called 'accessory molecules'. The physiologic role of some accessory molecules is to deliver signals to the T cells that function in concert with signals from the TCR complex to fully activate the cell.

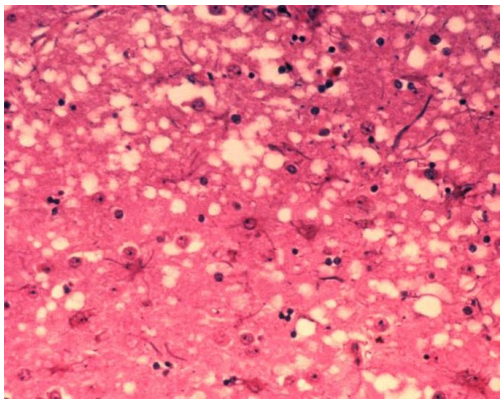

Figure: *Prion-affected tissue: This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic "holes" in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.*

The antigen receptor of MHC-restricted CD4 helper T cells and CD8 cytolytic T cell is a heterodimer consisting of two transmembrane polypeptide chains, designated alpha and beta, covalently linked to each other by disulfide bonds. Each alpha and beta chain consists of one variable domain (V), one constant domain (C), a hydrophobic transmembrane region, and a short cytoplasmic region. The V regions of the TCR contain short stretches of amino acids where the variability between different TCRs is concentrated, and these form the hypervariable or complementarity-determining regions (CDRs). The recognition of peptide-MHC complexes is mediated by CDRs formed by both the alpha and beta chains of the TCR.

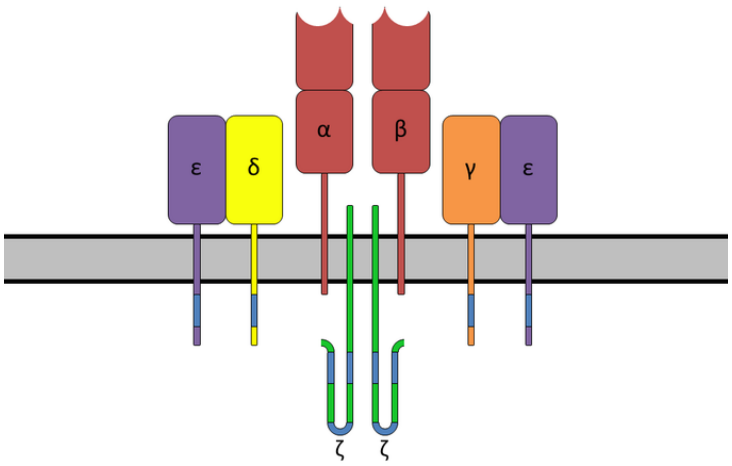

Figure: *T cell receptor: T cell receptor consists of alpha and beta chains, a transmembrane domain, and a cytoplasmic region.*

Key Points

- Many TCRs recognize the same antigen and many antigens are recognized by the same TCR.
- The TCR is composed of two different protein chains (that is, it is a heterodimer). In 95% of T cells, this consists of an alpha (α) and beta (β) chain, whereas in 5% of T cells this consists of gamma and delta (γ/δ) chains.
- When the TCR engages with antigen and MHC, the T lymphocyte is activated through a series of biochemical events mediated by associated enzymes, co- receptors, specialized accessory molecules, and activated or released transcription factors.

Key Terms

- polymorphic: relating to polymorphism (any sense), able to have several shapes or forms
- major histocompatibility complex: MHC is a cell surface molecule that mediate interactions of immune cells with other leukocytes or body cells. MHC determines compatibility of donors for organ transplants as well as one's susceptibility to an autoimmune disease. In humans, MHC is also called human leukocyte antigen (HLA).

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11.8F: Adaptive Immunity and the Immunoglobulin Superfamily

Learning Objectives

- Describe the role of immunoglobulins in the adaptive immune response, specifically in humoral immunity

Adaptive immunity is stimulated by exposure to infectious agents and increases in magnitude and defensive capabilities with each successive exposure to a particular microbe. The defining characteristics of adaptive immunity are specificity for distinct molecules and an ability to “remember” and respond more vigorously to repeated exposures to the same microbe.

The components of adaptive immunity are lymphocytes and their products. There are two types of adaptive immune responses: *humoral immunity* and *cell-mediated immunity.* These are driven by different elements of the immune system and function to eliminate different types of microbes. Protective immunity against a microbe may be induced by the host ‘s response to the microbe or by the transfer of antibodies or lymphocytes specific for the microbe. Antibodies or Immunoglobulins bind antigens in the recognition phase and the effector phase of humoral immunity.

The Immunoglobulin Superfamily

Immunoglobulins are produced in a membrane -bound form by B lymphocytes. These membrane molecules function as B cell receptors for antigens. The interaction of antigens with membrane antibodies on naive B cells initiates B cell activation. These activated B cells produce a soluble form of immunoglobulin that triggers effector mechanisms to eliminate antigens.

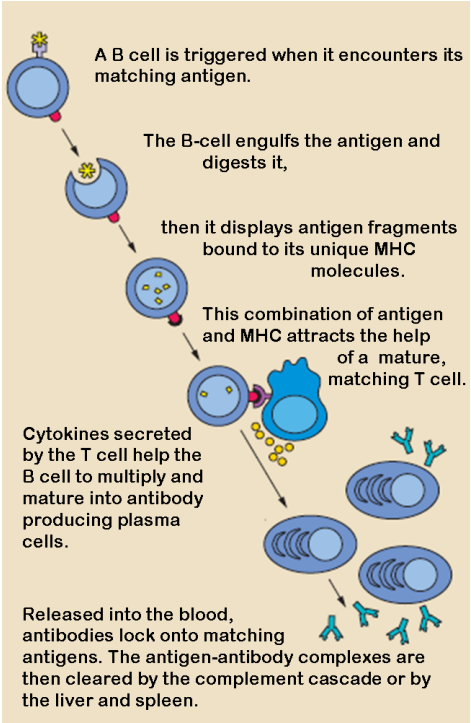

Figure: *B cell activation: When a B cell encounters its triggering antigen, it gives rise to many large cells known as plasma cells. Every plasma cell is essentially a factory for producing an antibody. Each of the plasma cells manufactures millions of identical antibody molecules and pours them into the bloodstream.*

These antibodies are part of a larger family called the i*mmunoglobulin superfamily*. The immunoglobulin superfamily (IgSF) is a large group of cell surface and soluble proteins that are involved in the recognition, binding, or adhesion processes of cells. Molecules are categorized as members of this superfamily based on structural features shared with immunoglobulins, which are also known as antibodies. They all possess a domain known as an *immunoglobulin domain* or *fold*. Members of the IgSF include cell surface antigen receptors, co-receptors, and co-stimulatory molecules of the immune system, molecules involved in antigen presentation to lymphocytes, cell adhesion molecules, certain cytokine receptors, and intracellular muscle proteins. They are commonly associated with roles in the immune system.

Key Points

- The concept of adaptive immunity suggests de novo generation in each individual of extremely large repertoires of diversified receptors and selective expansion of receptors that match the antigen /pathogen.
- Adaptive immune receptors of T and B lymphoid cells belong to the *immunoglobulin superfamily* and are created by rearrangement of gene segments.
- Immunoglobulins are glycoproteins in the immunoglobulin superfamily that function as antibodies.

Key Terms

- cytokine: Any of various small regulatory proteins that regulate the cells of the immune system.

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SECTION OVERVIEW

11.9: Antigen-Presenting Cells

Topic hierarchy

11.9A: Dendritic Cells

11.9B: Macrophages

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11.9A: Dendritic Cells

Dendritic cells are immune cells that function to process antigens and present them to T cells.

Learning Objectives

- Discuss the mechanism of action for dendritic cells

Key Points

- Dendritic cells function as antigen presenting cells.
- Dendritic cells are present in small quantities in tissues that are in contact with the external environment, mainly the skin (where there is a specialized dendritic cell type called Langerhans cells) and the inner lining of the nose, lungs, stomach and intestines.
- Once activated, dendritic cells migrate to the lymphoid tissues where they interact with T cells and B cells to initiate and shape the adaptive immune response.

Key Terms

- **lymphoid organs**: lymph nodes, spleen, and gut-associated lymphoid tissue where lymphocytes reside.

Dendritic cells are present in lymphoid organs, the epithelia of the skin, the gastrointestinal and respiratory tracts, and in most parenchymal organs. These cells are identified morphologically by their membranous projections that resemble spines. All dendritic cells are thought to arise from bone marrow precursors. Most, called myeloid dendritic cells, are related in lineage to mononuclear phagocytes. Immature dendritic cells (e.g. Langerhans cells of the epidermis) are located in main portals of entry of microbes (skin and gut epithelia). The function of epithelial dendritic cells is to capture microbial protein antigens and to transport the antigens to draining lymph nodes. During their migration to the lymph nodes, the dendritic cells mature to become extremely efficient at presenting antigens and stimulating naive T cells, hence their classification as antigen presenting cells. Mature dendritic cells reside in the T cell zones of the lymph nodes, and in this location they display antigens to T cells. Subsets of dendritic cells can be distinguished by the expression of cell surface markers. Different subpopulations of dendritic cells may stimulate distinct types of T cell effector responses. Some may even inhibit T cell activation.

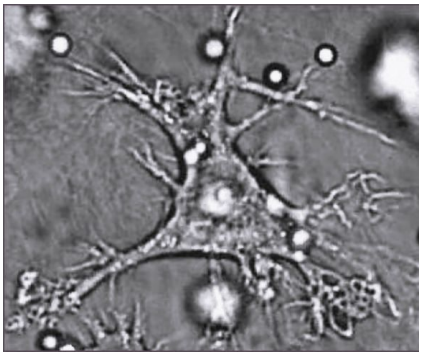

Figure: **Dendritic cell**: Dendritic cell characterized by membranous projections that resemble spines.

Dendritic cells are constantly in communication with other cells in the body. This communication can take the form of direct cell-to-cell contact based on the interaction of cell-surface proteins. An example of this includes the interaction of the membrane proteins of the B7 family of the dendritic cell with a CD28 cell surface molecule present on the lymphocyte. However, the cell-cell interaction can also take place at a distance via soluble factors such as cytokines. For example, stimulating dendritic cells *in vivo* with microbial extracts causes the dendritic cells to rapidly begin producing interleukin 12 (IL-12). IL-12 is a signal that helps differentiate naive CD4 T cells into a helper T cell phenotype. The ultimate consequence is priming and activation of the immune system for attack against the antigens which the dendritic cell presents on its surface.

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11.9B: Macrophages

Phagocytosis is a front-line defense against pathogen attack requiring the concerted action of macrophages.

Learning Objectives

- Describe the role of macrophages in the immune system

Key Points

- Macrophages are cells produced by the differentiation of monocytes in tissues.
- They are specialized phagocytic cells that attack foreign substances and infectious microbes through destruction and ingestion.
- Macrophages can be identified by specific expression of a number of proteins measured by flow cytometry or immunohistochemistry.

Key Terms

- **phagocyte**: A cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria and waste materials, or in the case of mature dendritic cells; displays antigens from invading pathogens to cells of the lymphoid lineage.
- **interferon-gamma**: a cytokine that is critical for innate and adaptive immunity against viral and intracellular bacterial infections.

Macrophages are antigen presenting cells that actively phagocytose large particles. Therefore, they play an important role in presenting antigens derived from phagocytosed infectious organisms such as bacteria and parasites. In the effector phase of cell-mediated immunity, differentiated effector T cells recognize microbial antigens on phagocytes and activate the macrophages to destroy these engulfed microbes. Most macrophages express high levels of interferon-gamma, a mechanism through which antigen presentation and T cell activation is enhanced. Macrophages can be identified by specific expression of a number of proteins including CD14, CD40, CD11b, F4/80(mice)/EMR1(human), lysozyme M, MAC-1/MAC-3 and CD68. They move by the action of amoeboid movement.

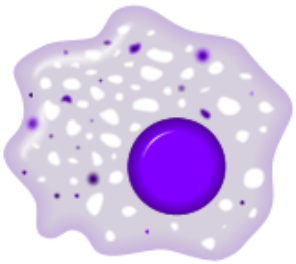

Figure: **Macrophage**: Macrophages are antigen presenting cells that engulf microbes.

Macrophages are not cells exclusive to the immune system; they also play a central function in many other aspects of embryonic development, homeostasis and wound repair. Resident macrophages become adapted to perform particular functions in different organs; so that brain macrophages (microglia) are very different from alveolar macrophages of the lung, Kupffer cells of the liver, or the largest tissue macrophage population, those lining the wall of the gut.

Monocytes are recruited into tissues in response to a very wide range of different stimuli. Where a pathogen is involved, they are commonly preceded by neutrophils, which release a range of toxic agents designed to kill extracellular pathogens. The macrophage then has the task of clearing both the dead pathogens and the dead neutrophils. To enter a tissue, the monocyte in peripheral blood must adhere to the vessel wall, cross the endothelial cell barrier, and then migrate towards the stimulus; a process known as chemotaxis.

The process of recruitment of neutrophils and macrophages involves the resident macrophages which act as sentinels. They respond to local stimuli by producing cytokines that make the endothelial cells more sticky (through the increased expression of cell adhesion molecules such as P-selectin) and so-called chemokines, that promote the directed migration of inflammatory cells. Monocytes may also migrate towards increasing concentrations of molecules produced by microorganisms themselves, by damaged tissues, or by the activation of the complement or clotting cascades which release bioactive peptides such as C5a.

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9.10A: Double-Stranded RNA Viruses - Retroviruses

Retroviruses are viruses that are able to reverse transcribe their RNA genome into DNA, which is then integrated into a host genome.

Learning Objectives

- Identify the unique features of retroviruses

Key Points

- In a double stranded RNA form, retroviruses infect a host cell with their genome, and then are reverse transcribed into double stranded DNA, with the DNA then integrated into the home cell genome.
- When integrated into a host genome, a retrovirus is hard to detect and can lay dormant for prolonged periods, having no discernible effect on the host.
- Retroviruses can be human pathogens, and cause many diseases, but have also proven to be invaluable tools when used by molecular biologists.

Key Terms

- **reverse transcriptase**: An enzyme that catalyzes the formation of DNA from RNA; found in retroviruses.
- **transposon**: A segment of DNA that can move to a different position within a genome.
- **integrase**: Any enzyme that integrates viral DNA into that of an infected cell.

A retrovirus is an RNA virus that is duplicated in a host cell using the reverse transcriptase enzyme to produce DNA from its RNA genome. The DNA is then incorporated into the host's genome by an integrase enzyme. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are enveloped viruses that belong to the viral family Retroviridae. A special variant of retroviruses are endogenous retroviruses, which are integrated into the genome of the host and inherited across generations. Endogenous retroviruses are a type of transposon.

The virus itself stores its nucleic acid in the form of an mRNA genome and serves as a means of delivering that genome into cells it targets as an obligate parasite (a parasite that cannot live without its host). That process of delivering the genome into cells constitutes the infection. Once in the host's cell, the RNA strands undergo reverse transcription in the cytoplasm and are integrated into the host's genome, at which point the retroviral DNA is referred to as a provirus. It is difficult to detect the virus until it has infected the host, where the provirus can stay for months, even years, before becoming active and making new infectious viral particles.

In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein. Retroviruses, however, function differently. Their RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translation processes to express the genes carried by the virus. So, the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → protein. Retroviruses can be pathogens of many different hosts, including humans. A notable retrovirus is Human immunodeficiency virus (HIV), the virus responsible for acquired immunodeficiency syndrome (AIDS). As well as infecting a host, some retroviruses can cause cancer.

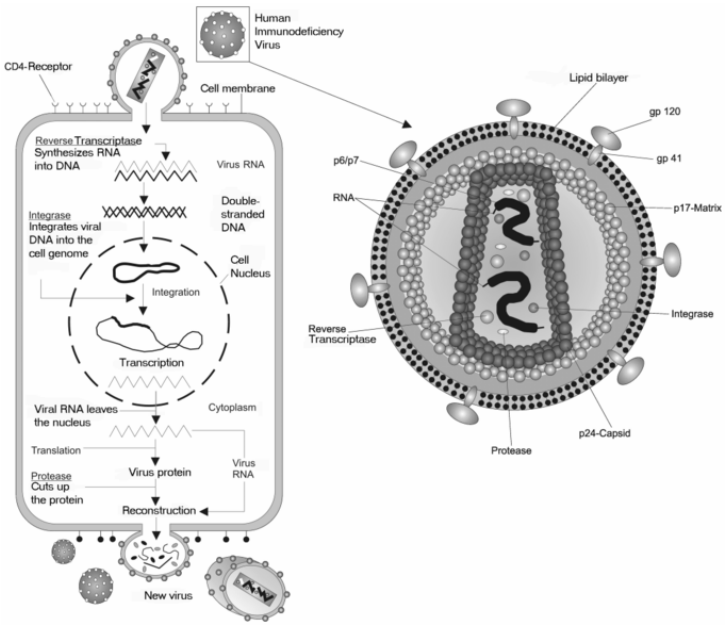

Figure: **HIV viral life cycle**: This diagram depicts the viral life cycle of HIV, from infection, integration into a host genome, reconstruction, and formation of new viral particles. The inset on the left depicts an individual HIV particle.

Finally, retroviruses are proving to be valuable research tools in molecular biology and have been successfully used in gene delivery systems.

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9.10B: HIV Attachment and Host Cell Entry

The attachment and fusion of HIV virons to host cells are crucial to HIV infection.

Learning Objectives

- Define the unique aspects of HIV attachment and host cell entry

Key Points

- HIV proteins bind to specific receptors of host cells, most importantly HIV coat proteins gp41 and gp160.
- After attaching to the host, many of the receptors on both the cell and invading virus bind together for fusion of the virus with its host.
- Because HIV attachment is critical for the HIV replication cycle, understanding the specific mechanisms by which HIV attachment occurs has implications for potential treatments of HIV.

Key Terms

- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **capsid**: The outer protein shell of a virus.
- **chemokine**: Any of various cytokines, produced during inflammation, that organize the leukocytes.
- **T cells**: A lymphocyte, from the thymus, that can recognise specific antigens and can activate or deactivate other immune cells.

HIV entry is the earliest stage of infection in the HIV viral life cycle, occurring when the HIV virus comes into contact with the host cell and introduces viral material into the cell. HIV enters macrophages and CD4-positive T cells (CD4 is a glycoprotein receptor found on cells) by the adsorption of glycoproteins on its surface to receptors on the target cell, followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell.

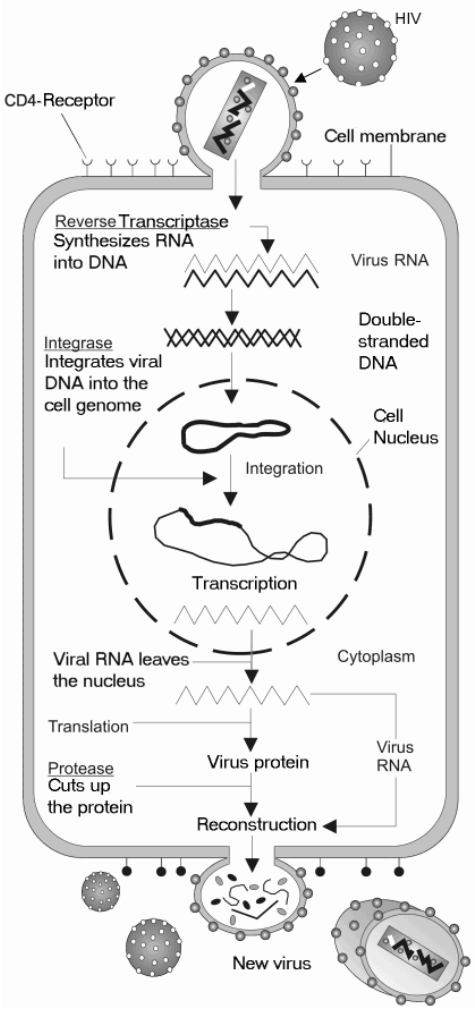

Figure: **HIV Replication**: Steps in the HIV Replication Cycle: Fusion of the HIV cell to the host cell surface.Cell Entry, HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.Viral DNA is formed by reverse transcription.Viral DNA is transported across the nucleus and integrates into the host DNA.New viral RNA is used as genomic RNA to make viral proteins.New viral RNA and proteins move to cell surface and a new, immature, HIV virus forms.Virus maturation and protease release of individual HIV proteins.

Entry to the cell begins through interaction of the trimeric envelope complex and both CD4 and a chemokine receptor on the host cell on the cell surface. The HIV coat protein, gp120, binds to integrin α4β7, activating LFA-1 (the central integrin involved in the establishment of bridges known as “virological synapses”) which facilitate efficient cell-to-cell spreading of HIV-1.

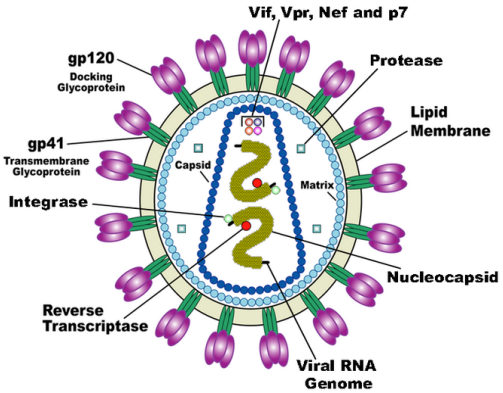

Figure: **Origin of HIV-1 M: An Example of Molecular Clock Application**: The attachment and fusion of HIV virons to host cells are crucial to allowing HIV infection to occur. Shown in purple is gp120 and in green gp41, two proteins crucial in viral docking to host cells.

After attachment, the HIV viron must next fuse with the host cell. The first step in fusion begins after the attachment of the CD4 binding domains of gp120 to CD4. Once gp120 is bound with the CD4 protein, the envelope complex undergoes a structural change, exposing the chemokine binding domains of gp120 and allowing them to interact with the target chemokine receptor. This allows for a more stable two-pronged attachment, which allows the N-terminal fusion peptide gp41 to penetrate the cell membrane. Repeat sequences in gp41, known as HR1 and HR2, then interact, causing the collapse of the extracellular portion of gp41 into a hairpin. This loop structure brings the virus and cell membranes close together, allowing fusion of the membranes and subsequent entry of the viral capsid.

After HIV has bound to the target cell, the HIV RNA and various enzymes (including reverse transcriptase, integrase, ribonuclease, and protease) are injected into the cell. Because HIV attachment is critical for the HIV replication cycle, understanding the specific mechanisms through which HIV attachment occurs has implications for potential treatments of HIV.

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9.10C: Retroviral RNA Genome

Learning Objectives

- Discover the features of retroviral genomes

The retroviral while in the viral capsid consists of a dimer RNA. It has a cap at the 5′ end and a poly(A) tail at the 3′ end. The RNA genome also has terminal noncoding regions, which are important in replication, and internal regions that encode virion proteins for gene expression.

The 5′ end includes four regions, which are R, U5, PBS, and L.

- The R region is a short repeated sequence at each end of the genome during the reverse transcription in order to ensure correct end-to-end transfer in growing chain.
- U5, on the other hand, is a short unique sequence between R and PBS.
- PBS (primer binding site) consists of 18 bases complementary to 3′ end of the tRNA primer, which supplies an ‘OH group to initiate reverse transcription.
- The L region is an untranslated leader region that give the signal for packaging of genome RNA.

The 3′ end includes 3 regions, which are PPT (polypurine tract), U3, and R.

- PPT (or PP), polypurine tract is the primer for plus-strand DNA synthesis during reverse transcription.
- U3 is a sequence between PPT and R, which has signal that provirus can use in transcription.
- R is the terminal repeated sequence at 3′ end, the same as the R (i.e., repeat region of the 5′ end).

Inbetween the 5′ and 3′ region is the protein encoding region of the retrovirus, consisting of gag proteins, protease (PR), pol proteins and env proteins. Gag proteins are major components of the viral capsid, which are about 2,000-4,000 copies per virion. Protease is expressed differently in different viruses. It functions in proteolytic cleavages during virion maturation to make mature gag and pol proteins. Pol proteins, such as the reverse transcriptase (RT), are responsible for synthesis of viral DNA and integration into host DNA after infection. Finally, env proteins play a role in association and entry of virion into the host cell. Possessing a functional copy of an env gene is what makes retroviruses distinct from retroelements. The env gene serves three distinct functions: enabling the retrovirus to enter/exit host cells through endosomal membrane trafficking, protection from the extracellular environment via the lipid bilayer, and the ability to enter cells. The ability of the retrovirus to bind to its target host cell using specific cell-surface receptors is given by the surface component (SU) of the env, while the ability of the retrovirus to enter the cell via membrane fusion is imparted by the membrane-anchored trans-membrane component (TM). Thus, the env protein is what enables the retrovirus to be infectious.

Please refer to the figure, in it you see all the elements of a retroviral genome and how they interact to contribute to retroviral reverse transcription and integration.

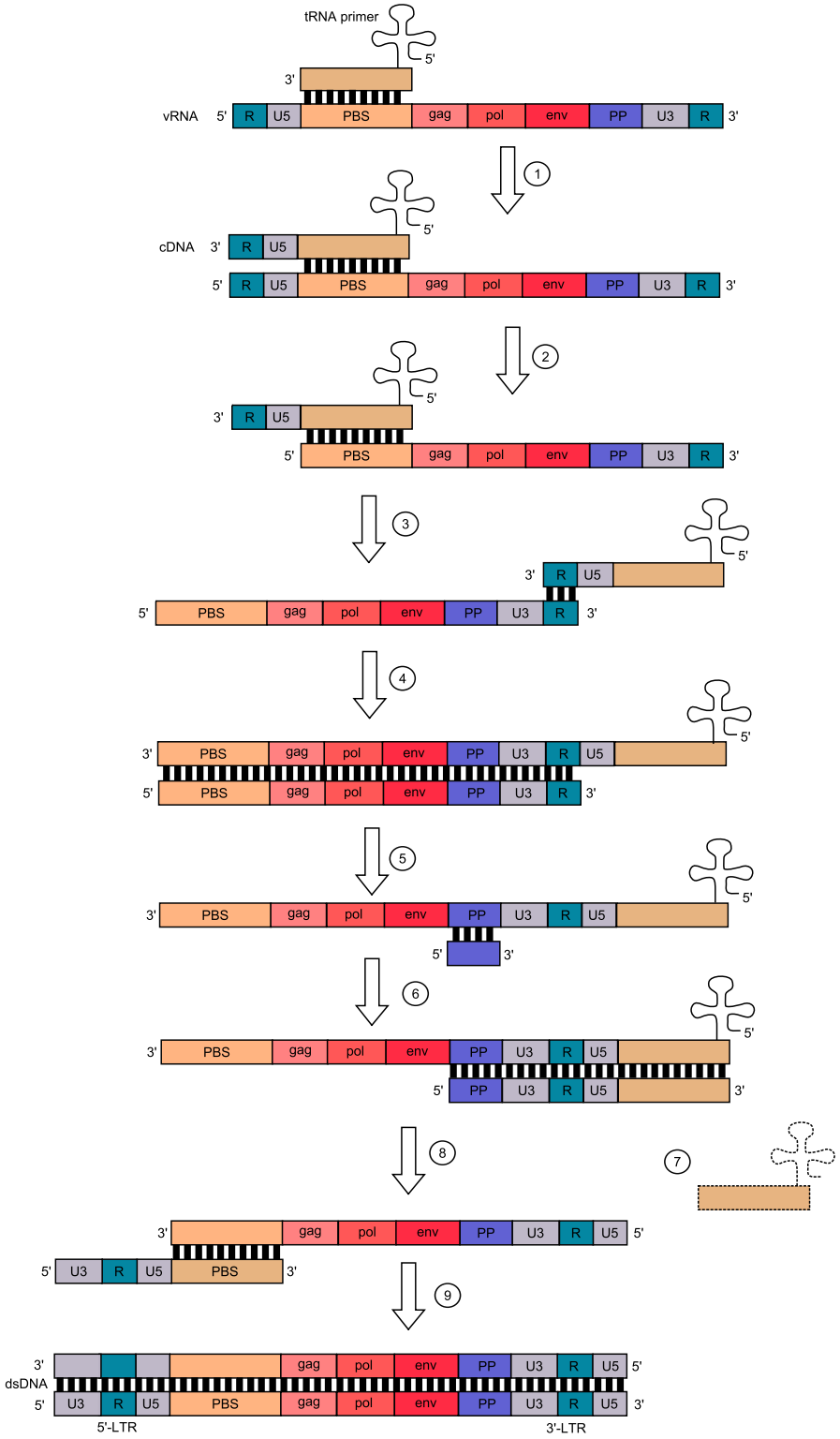

Figure: ***Retroviral genome****: Through the mechanism of reverse transcription by human immunodeficiency virus (HIV), we see what the different genomic elements of a retrovirus are. Reverse transcription occurs in the cytoplasm of host cell. In this process, viral ssRNA is transcribed by the viral reverse transcriptase (RT) into double stranded DNA. Reverse transcription takes place in 5'→3' direction. tRNA ("cloverleaf") hybridizes to PBS and provides -OH group for initiation of reverse transcription. 1) Complementary DNA (cDNA) is formed. 2) Template in RNA:DNA hybrid is degraded by RNase H domain of reverse transcriptase 3) DNA:tRNA is transferred to the 3'-end of the template. 4) First strand synthesis takes place. 5) The rest of viral ssRNA is degraded by RNase H, except for the PP site. 6) Synthesis of second strand of ssDNA is initiated from the 3'-end of the template. tRNA is necessary to synthesis of complementary PBS 7) tRNA is degraded 8) PBS from the second strand hybridizes with the complementary PBS on the first strand. 9) Synthesis of both strands is completed by the DNA Polmerase function of reverse transcriptase. Both dsDNA*

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ends have U3-R-U5 sequences, so called long terminal repeat sequences (3'LTR and 5'LTR, respectively). LTRs mediate integration of the retroviral DNA into another region of the host genome.Key: U3 – promoter region, U5 – recognition site for viral integrase; PBS – primer binding site; PP – polypurine section (polypurine tract); gag, pol, and env. Colors mark complementary sequences.

Key Points

- The ends of a retrovirus, both the 5′ and 3′, contain many elements needed for the retroviral life cycle, including the regions referred to as R, U5, PBS, PPT, and U3.
- In between the 5′ and 3′ ends is the protein coding region which includes the gag, pol, and env encoding regions.
- Key to the unique attributes of a retrovirus is the pol region, which encodes a reverse trancriptase (RT), RT is the enzyme which takes the RNA form of the retrovirus genome and converts into DNA, the DNA form of which can integrate into the host genome.

Key Terms

- **protease**: An enzyme that cuts or cleaves proteins.
- **capsid**: The outer protein shell of a virus.

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9.10D: Replicative Cycle of HIV

Learning Objectives

- Compare and contrast HIV replication to other viruses

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS). AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. HIV can infect dendritic cells (DCs). DCs are one of the first cells encountered by the virus during sexual transmission. They are currently thought to play an important role by transmitting HIV to T-cells when the virus is captured in the mucosa by DCs. HIV enters macrophages and T cells by the adsorption of glycoproteins on its surface to receptors on the target cell. This is followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell.

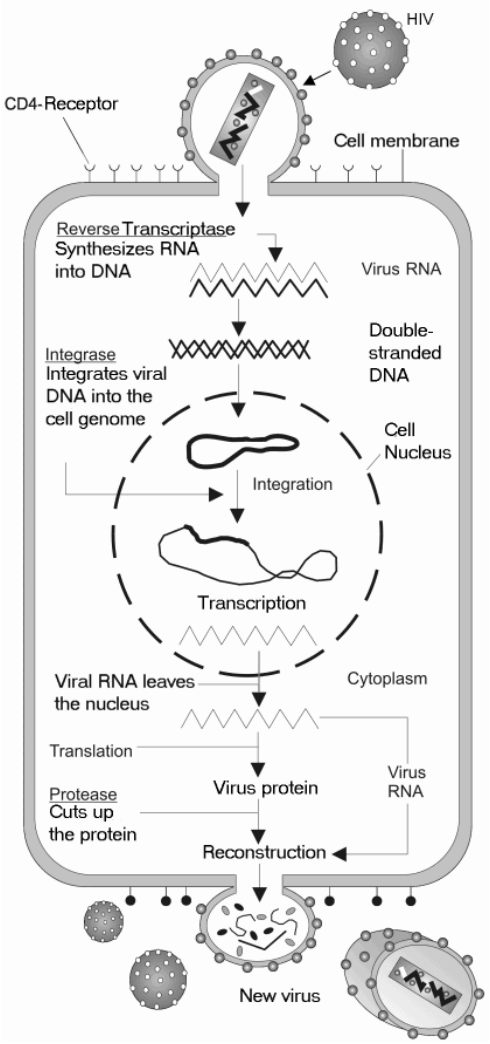

Figure: ***HIV Replication****: Steps in the HIV Replication Cycle: Fusion of the HIV cell to the host cell surface.Cell Entry, HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.Viral DNA is formed by reverse transcription.Viral DNA is transported across the nucleus and integrates into the host DNA.New viral RNA is used as genomic RNA to make viral proteins.New viral RNA and proteins move to cell surface and a new, immature, HIV virus forms.Virus maturation and protease release of individual HIV proteins.*

Shortly after the viral capsid enters the cell, an enzyme called reverse transcriptase liberates the single-stranded (+)RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA) molecule. The process of reverse transcription is extremely error-prone, and the resulting mutations may cause drug resistance or allow the virus to evade the body's immune system. The reverse transcriptase also has ribonuclease activity that degrades the viral RNA during the synthesis of cDNA, as well

as DNA-dependent DNA polymerase activity that creates a sense DNA from the antisense cDNA. Together, the cDNA and its complement form a double-stranded viral DNA that is then transported into the cell nucleus.

This integrated viral DNA may then lie dormant, in the latent stage of HIV infection. To actively produce the virus, certain cellular transcription factors need to be present. The most important of these is NF-κB (NF kappa B), which is upregulated when T-cells become activated. This means that those cells most likely to be killed by HIV are those currently fighting infection. During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the regulatory proteins Tat (which encourages new virus production) and Rev.

As the newly produced Rev protein accumulates in the nucleus, it binds to viral mRNAs and allows unspliced RNAs to leave the nucleus, where they are otherwise retained until spliced. At this stage, the structural proteins Gag and Env are produced from the full-length mRNA. The full-length RNA is actually the virus genome; it binds to the Gag protein and is packaged into new virus particles. The final step of the viral cycle, assembly of new HIV-1 virions, begins at the plasma membrane of the host cell. The Env polyprotein goes through the endoplasmic reticulum and is transported to the Golgi complex. There, it is cleaved by HIV protease and processed into the two HIV envelope glycoproteins, gp41 and gp120. These are transported to the plasma membrane of the host cell where gp41 anchors gp120 to the membrane of the infected cell. The Gag (p55) and Gag-Pol (p160) polyproteins also associate with the inner surface of the plasma membrane along with the HIV genomic RNA as the forming virion begins to bud from the host cell.

Maturation occurs either in the forming bud or in the immature virion after it buds from the host cell. During maturation, HIV proteases cleave the polyproteins into individual functional HIV proteins. This cleavage step can be inhibited by protease inhibitors. The various structural components then assemble to produce a mature HIV virion. The mature virion is then able to infect another cell.

Key Points

- First the HIV viron binds to host cell, after binding the virus and cell fuse, which releases the various enzymes HIV needs to reverse transcribe and integrate into the host genome.
- The reverse transcription of HIV viral RNA to DNA is error prone, causing HIV to have a high mutation rate. This makes it difficult to design treatments against HIV.
- The HIV provirus can stay dormant in the host genome for years. It may become active when the host T cell is itself activated by fighting an infection that the body is facing.
- Understanding the HIV life cycle will help in providing effective treatments against HIV.

Key Terms

- **provirus**: A virus genome, such as HIV, that integrates itself into the DNA of a host cell so as to be passively replicated along with the host genome.
- **reverse transcriptase**: An enzyme that catalyzes the formation of DNA from RNA; found in retroviruses.

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SECTION OVERVIEW

9. 11: DNA Viruses in Eukaryotes

Topic hierarchy

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9.11B: Replication of Double-Stranded DNA Viruses of Animals

9.11C: Double-Stranded DNA Viruses - Herpesviruses

9.11E: Attachment and Entry of Herpes Simplex

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9.11J: Treatment of Animal Viral Infections

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9.11A: Plant DNA Viruses

DNA viruses are relatively rare in plants, but are responsible for a significant amount of crop damage worldwide.

Learning Objectives

- Differentiate between ssDNA and dsDNA plant viruses

Key Points

- DNA viruses are relatively rare in plants, compared to their RNA counterparts.
- Like most viruses, the genomes of most single stranded DNA viruses are small, encoding only a few proteins, and are therefore dependent on host cell factors for replication.
- Double stranded DNA viruses only infect lower species of plants, such as algae. These viruses are huge dsDNA viruses with genomes ranging from 160 to 560 kb with up to 600 protein-encoding genes, making them distinctly different from viruses infecting higher plants.
- Plant viruses are generally spread through vectors, such as insects, but can also be passed from generation to generation.

Key Terms

- **Baltimore Classification System**: The Baltimore classification, developed by David Baltimore, is a virus classification system that groups viruses into families, depending on their type of genome (DNA, RNA, single-stranded (ss), double-stranded (ds), etc.) and their method of replication.
- **plasmodesmata**: Plasmodesmata (singular: plasmodesma) are microscopic channels which traverse the cell walls of plant cells and some algal cells, enabling transport and communication between them.
- **capsid**: The outer protein shell of a virus.

A DNA virus is a virus with DNA as its genetic material and replicates using a DNA-dependent DNA polymerase. DNA viruses belong to either Group I (double-stranded DNA; dsDNA) or Group II (single-stranded DNA; ssDNA) of the Baltimore classification system for viruses. Single-stranded DNA is usually expanded to double-stranded in infected cells.

DNA viruses are relatively rare in plants. Seventeen percent of plant viruses are ssDNA, while dsDNA viruses infect only lower plants, such as eukaryotic algae. The rarity of dsDNA plant viruses is notable when compared to other taxonomic kingdoms; a quarter of animal viruses and three quarters of bacterial viruses are dsDNA.

Plant viruses are transmitted through a variety of different methods, and generally require breach of protective barriers. Viruses can be spread by direct transfer of sap by contact of a wounded plant with a healthy one, most commonly resulting from agricultural practices, as by damage caused by tools or hands. More often, viruses are spread through vector intermediaries such as insects, nematodes, or protozoa which pick up viruses by feeding on infected plants, and then spread the virus to healthy plants.

Viral transmission from generation to generation occurs in about 20% of plant viruses. When viruses are transmitted by seeds, the seed is infected in the generative cells and the virus is maintained in the germ cells, or occasionally in the seed coat. Little is known about the mechanisms involved in the transmission of plant viruses via seeds, though environment is known to play a key role.

Single-Stranded DNA Viruses

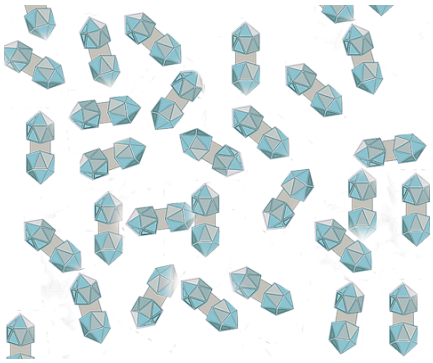

Figure: **Geminiviruses**: Drawing of geminiviruses, characterized by elongated, geminate capsids with two incomplete T=1 icosahedra joined at the missing vertex.

The *Geminiviridae* and *Nanoviridae* are the two families of ssDNA viruses known to infect plants. *Geminiviridae* is the largest known family of single-stranded DNA viruses. It contains a wide range of plant viruses including bean golden mosaic virus, beet curly top virus, maize streak virus, and tomato pseudo-curly top virus, which together are responsible for a significant amount of crop damage worldwide. The genome can either be a single component between 2500-3100 nucleotides, or, in the case of some begomoviruses, two similar-sized components each between 2600 and 2800 nucleotides. They have elongated, geminate capsids with two incomplete T=1 icosahedra joined at the missing vertex. The capsids range in size from 18-20 nm in diameter with a length of about 30 nm. Begomoviruses possess two component genomes separated into two different particles, both of which must usually be transmitted together to initiate a new infection within a suitable host cell. Like many viruses, geminivirus genomes encode only a few proteins, and are therefore dependent on host cell factors for replication. Geminiviruses replication occurs within the nucleus of an infected plant cell via a rolling circle mechanism, similar to that seen in bacteriophages, such as M13, and many plasmids. The resulting ssDNA is packaged into germinate particles in the nucleus. It is not clear if these particles can then leave the nucleus and be transmitted to surrounding cells as virions, or whether ssDNA is trafficked from cell to cell via the plasmodesmata. These viruses tend to be introduced into and initially infect differentiated plant cells, via the piercing mouthparts of the vector insect: however, these cells generally lack the host enzymes necessary for DNA replication, making it difficult for the virus to replicate. To overcome this block geminiviruses can induce plant cells to reenter the cell cycle from a quiescent state so that viral replication can occur.

The *Nanoviridae* are a family of single-stranded DNA viruses that infect plants. Their name is derived from the Greek word ‘nano’ (dwarf) because of their small genome and their stunting effect on infected plants.



Figure: **Maize Streak Virus**: The black-faced leafhopper (Graminella nigrifrons) transmits both maize fine streak virus and maize chlorotic dwarf virus.

Virions of this family have a capsid and are non-enveloped. The capsid is icosahedral with diameter of 18-20 nm. The genome is composed of 6 to 11 segments of single-stranded circular DNA each ~1 kb in length, with the exact number of segments varying depending on the genus. The segments each encode a single protein. There is a putative stem loop structure in the non-coding region of each segment which has a conserved 9-nucleotide sequence at its apex. Each member has up to 4 segments encoding replication proteins of ~33 kDa. The other segments encode products of 10-20 kDa in size and include a coat protein of ~19 kDa and a protein with a retinoblastoma binding motif.

Double-Stranded DNA Viruses

Double-stranded DNA viruses of plants are rare, and only infect lower plants, such as algae. These viruses (family *Phycodnaviridae*) are huge dsDNA viruses with genomes ranging from 160 to 560 kb with up to 600 protein-encoding genes, making them distinctly different from viruses infecting higher plants. They are found in aqueous environments throughout the world and play dynamic, albeit largely undocumented, roles in regulating algal communities such as the termination of massive algal blooms commonly referred to as red and brown tides.

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9.11B: Replication of Double-Stranded DNA Viruses of Animals

Most double-stranded DNA viruses replicate within the host cell nucleus.

Learning Objectives

- Differentiate the ways which different classes of dsDNA viruses replicate

Key Points

- From the perspective of the virus, the purpose of viral replication is to allow production and survival of its kind.
- Most double-stranded DNA viruses replicate within the host cell nucleus, including polyomaviruses, adenoviruses, and herpesviruses—poxviruses, however, replicate in the cytoplasm.
- Adenoviruses and herpes viruses encode their own replication factors.

Key Terms

- **Okazaki fragments**: Okazaki fragments are short, newly synthesized DNA fragments that are formed on the lagging template strand during DNA replication.
- **polymerase**: Any of various enzymes that catalyze the formation of polymers of DNA or RNA using an existing strand of DNA or RNA as a template.

Viral replication is the formation of biological viruses during the infection process in the target host cells. Viruses must first get into the cell before viral replication can occur. From the perspective of the virus, the purpose of viral replication is to allow production and survival of its kind. By generating abundant copies of its genome and packaging these copies into viruses, the virus is able to continue infecting new hosts. Replication between viruses is greatly varied and depends on the type of genes involved in them. Most DNA viruses assemble in the nucleus while most RNA viruses develop solely in cytoplasm.

Double-stranded DNA viruses usually must enter the host nucleus before they are able to replicate. Some of these viruses require host cell polymerases to replicate their genome, while others, such as adenoviruses or herpes viruses, encode their own replication factors. However, in either cases, replication of the viral genome is highly dependent on a cellular state permissive to DNA replication and, thus, on the cell cycle. The virus may induce the cell to forcefully undergo cell division, which may lead to transformation of the cell and, ultimately, cancer. An example of a family within this classification is the Adenoviridae.

Polyomaviruses, adenoviruses, and herpesviruses are all nuclear-replicating DNA viruses, each with their own specific approaches to replication. There is only one well-studied example in which a double-stranded DNA virus does not replicate within the nucleus. This is the Poxvirus family, which comprises highly pathogenic viruses that infect vertebrates.

Polyomaviruses

Polyomaviridae is a family of viruses whose natural hosts are primarily mammals and birds. Most of these viruses, such as BK virus and JC virus, are very common and typically asymptomatic in most human populations studied. However, some polyomaviruses are associated with human disease, particularly in immunocompromised individuals. Some members of the family are oncoviruses, meaning they can cause tumors; they often persist as latent infections in a host without causing disease, but may produce tumors in a host of a different species, or in individuals with ineffective immune systems. The name polyoma refers to the viruses' ability to produce multiple (poly-) tumors (-oma).

Replication

Prior to genome replication, the processes of viral attachment, entry and uncoating occur. Polyomavirus virions are subsequently endocytosed and transported first to the endoplasmic reticulum where a conformational change occurs; then by an unknown mechanism the virus is exported to the nucleus. Polyomaviruses replicate in the nucleus of the host.

Adenoviruses

Adenoviruses (members of the family Adenoviridae) are medium-sized (90–100 nm), nonenveloped (without an outer lipid bilayer) viruses with an icosahedral nucleocapsid containing a double stranded DNA genome.

Adenoviruses represent the largest nonenveloped viruses. They are able to be transported through the endosome (i.e., envelope fusion is not necessary). The virion also has a unique "spike" or fiber associated with each penton base of the capsid that aids in

attachment to the host cell via the receptor on the surface of the host cell.

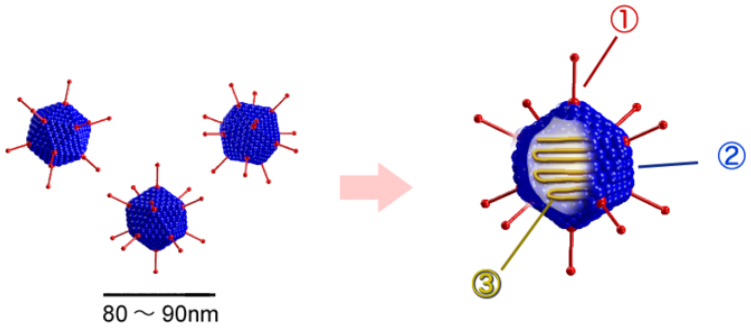

Figure: **Adenovirus structure**: Adenoviruses are non-enveloped (i.e., they have no external lipid bilayer) and are icosahedral (i.e., shaped like a polyhedron with 20 faces). They have fibers at their vertices that help them attach to host cells.

Replication

Adenoviruses possess a linear dsDNA genome and are able to replicate in the nucleus of vertebrate cells using the host's replication machinery.

Once the virus has successfully gained entry into the host cell, the endosome acidifies, which alters virus topology by causing capsid components to disband, which in turn destroys the endosome and allows the virion entry into the cytoplasm. It is transported to the nuclear pore, disassembles, and is released into the nucleus. At this point viral gene expression can occur and new virus particles can be generated.

Herpesviruses

Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans. The members of this family are also known as herpesviruses. The family name is derived from the Greek word herpein ("to creep"), referring to the latent, recurring infections typical of this group of viruses. Herpesviridae can cause latent or lytic infections.

At least five species of Herpesviridae – HSV-1 and HSV-2 (both of which can cause orolabial herpes and genital herpes), Varicella zoster virus (which causes chicken-pox and shingles), Epstein-Barr virus (which causes mononucleosis), and Cytomegalovirus – are extremely widespread among humans. More than 90% of adults have been infected with at least one of these, and a latent form of the virus remains in most people. In total, there are 8 herpesvirus types that infect humans: herpes simplex viruses 1 and 2, varicella-zoster virus, EBV (Epstein-Barr virus), human cytomegalovirus, human herpesvirus 6, human herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus. There are more than 130 herpesviruses, and some are from mammals, birds, fish, reptiles, amphibians, and molluscs.

Replication

All herpesviruses are nuclear-replicating—the viral DNA is transcribed to mRNA within the infected cell's nucleus. Infection is initiated when a viral particle contacts a cell with specific types of receptor molecules on the cell surface. Following binding of viral envelope glycoproteins to cell membrane receptors, the virion is internalized and dismantled, allowing viral DNA to migrate to the cell nucleus. Within the nucleus, replication of viral DNA and transcription of viral genes occurs.

Poxviruses

Poxviridae is a family of viruses. Human, vertebrates, and arthropods serve as natural hosts. There are currently 69 species in this family, divided among 28 genera, which are divided into two subfamilies. Diseases associated with this family include smallpox.

Poxviridae viral particles (virions) are generally enveloped (external enveloped virion- EEV), though the intracellular mature virion (IMV) form of the virus, which contains different envelope, is also infectious. The virion is exceptionally large—around 200 nm in diameter and 300 nm in length.

Replication

The replication of poxvirus is unusual for a virus with double-stranded DNA genome (dsDNA) because it occurs in the cytoplasm, although this is typical of other large DNA viruses. Poxvirus encodes its own machinery for genome transcription, a DNA dependent RNA polymerase, which makes replication in the cytoplasm possible. Most dsDNA viruses require the host cell's DNA-dependent RNA polymerase to perform transcription. These host DNA are found in the nucleus, and therefore most dsDNA viruses carry out a part of their infection cycle within the host cell's nucleus.

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9.11C: Double-Stranded DNA Viruses - Herpesviruses

Herpes viruses cause a wide range of latent, recurring infections including oral and genital herpes, cytomegalovirus, and chicken pox.

Learning Objectives

- Recognize the attributes of herpes viruses

Key Points

- Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans.
- The structure of herpes viruses consists of a relatively large double-stranded, linear DNA genome encased within an icosahedral protein cage called the capsid, which is wrapped in a lipid bilayer called the envelope.
- Notable herpes viruses include herpes simplex viruses 1 and 2, Varicella zoster virus (the causative agent of shingles and chicken pox), cytomegalovirus, and Kaposi's sarcoma virus.
- There is no method to eradicate herpes virus from the body, but antiviral medications, such as acyclovir, can reduce the frequency, duration, and severity of outbreaks.

Key Terms

- **tegument**: A natural covering of the body or of a bodily organ.
- **capsid**: The outer protein shell of a virus.
- **virion**: A single individual particle of a virus (the viral equivalent of a cell).

Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans. The members of this family are also known as herpes viruses. The family name is derived from the Greek word *herpein* ("to creep"), referring to the latent, recurring infections typical of this group of viruses.

Animal herpes viruses all share some common properties. The structure of these viruses consists of a relatively large double-stranded, linear DNA genome encased within an icosahedral protein cage called the capsid, which is wrapped in a lipid bilayer called the envelope. The envelope is joined to the capsid by means of a tegument. This complete particle is known as the virion. HSV-1 and HSV-2 each contain at least 74 genes within their genomes, although speculation over gene crowding allows as many as 84 unique protein-coding genes by 94 putative pen reading frames. These genes encode a variety of proteins involved in forming the capsid, tegument and envelope of the virus, as well as controlling the replication and infectivity of the virus.

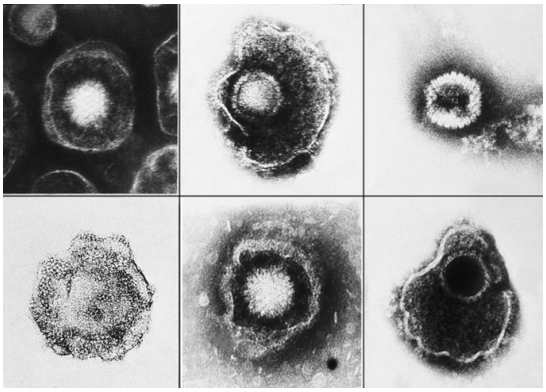

Figure: **Herpesviridae**: Various viruses from the Herpesviridae family seen using an electron micrograph Amongst these members is varicella-zoster (Chickenpox), and herpes simplex type 1 and 2 (HSV-1, HSV-2).

Types of herpes viruses

There are nine distinct herpes viruses which cause disease in humans:

- HHV-1 Herpes simplex virus-1 (HSV-1)
- HHV-2 Herpes simplex virus-2 (HSV-2)
- HHV-3 Varicella zoster virus (VZV)
- HHV-4 Epstein-Barr virus (EBV)

- HHV-5 Cytomegalovirus (CMV)
- HHV-6A/B Roseolovirus, Herpes lymphotropic virus
- HHV-7 Pityriasis Rosea
- HHV-8 Kaposi's sarcoma-associated herpesvirus

Of particular interest include HSV-1 and HSV-2, which cause oral and/or genital herpes, HSV-3 which causes chickenpox and shingles, and HHV-5 which causes mononucleosis-like symptoms, and HHV-8 which causes a Kaposi's sarcoma, a cancer of the lymphatic epithelium.

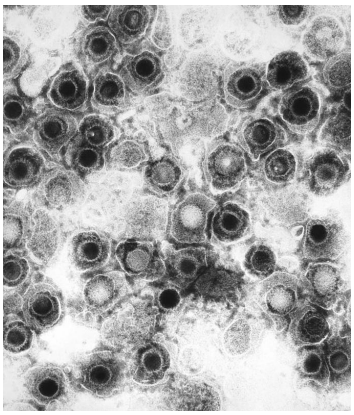

Figure: **Herpes Simplex Virions**: This negatively-stained transmission electron micrograph (TEM) revealed the presence of numerous herpes simplex virions, members of the Herpesviridae family. There are two strains of the herpes simplex virus, HSV-1, which is responsible for cold sores, and HSV-2, which is responsible for genital herpes. At the core of its icosahedral proteinaceous capsid, the HSV contains a double-stranded DNA linear genome.

Infection is caused through close contact with an infected individual. Infection is initiated when a viral particle comes in contact with the target cell specific to the individual herpes virus. Viral glycoproteins bind cell surface receptors molecules on the cell surface, followed by virion internalization and disassembly. Viral DNA then migrates to the cell nucleus where replication of viral DNA and transcription of viral genes occurs.

During symptomatic infection, infected cells transcribe lytic viral genes. In some host cells, a small number of viral genes termed *latency-associated transcripts* accumulate instead. In this fashion, the virus can persist in the cell (and thus the host) indefinitely. While primary infection is often accompanied by a self-limited period of clinical illness, long-term latency is symptom-free.

Reactivation of latent viruses

This has been implicated in a number of diseases (e.g. Shingles, Pityriasis Rosea). Following activation, transcription of viral genes transitions from latency-associated transcripts to multiple lytic genes; these lead to enhanced replication and virus production. Often, lytic activation leads to cell death. Clinically, lytic activation is often accompanied by emergence of non-specific symptoms such as low grade fever, headache, sore throat, malaise, and rash, as well as clinical signs such as swollen or tender lymph nodes, and immunological findings such as reduced levels of natural killer cells.

There is no method to eradicate the herpes virus from the body, but antiviral medications, such as *acyclovir*, can reduce the frequency, duration, and severity of outbreaks. Analgesics such as *ibuprofen* and *acetaminophen* can reduce pain and fever. Topical anesthetic treatments such as *prilocaine*, *lidocaine*, *benzocaine* or *tetracaine* can also relieve itching and pain.

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9.11E: Attachment and Entry of Herpes Simplex

Herpes simplex virus attaches to a host's cells with viral envelope glycoproteins, which then allows entry of the viral capsid into the host cell.

Learning Objectives

- Illustrate HSV attachment to host cells

Key Points

- The genome encodes for 11 different glycoproteins, four of which, gB, gC, gD and gH, are involved in viral attachment.
- The sequential stages of HSV entry are analogous to those of other viruses.
- First, complementary viral and cell surface receptors bring the viral and host cell membranes into close proximity. Next, the two membranes begin to merge, forming a hemifusion state. Finally, a stable entry pore is formed through which the viral envelope contents are introduced to the host cell.

Key Terms

- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **hemifusion**: Partial fusion, or the first stage in full fusion.
- **heparan sulfate**: A polysaccharide found, associated with protein, in all animal tissue; it has a regulatory function in several biological activities.

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are two members of the herpes virus family, *Herpesviridae*, that infect humans. Both HSV-1 (which produces most cold sores) and HSV-2 (which produces most genital herpes) are ubiquitous and contagious. They can be spread when an infected person is producing and shedding the virus.

The sequential stages of HSV entry are analogous to those of other viruses. At first, complementary receptors on the virus and the cell surface bring the viral and cell membranes into close proximity. In an intermediate state, the two membranes begin to merge, forming a hemifusion state. Finally, a stable entry pore is formed through which the viral envelope contents are introduced to the host cell.

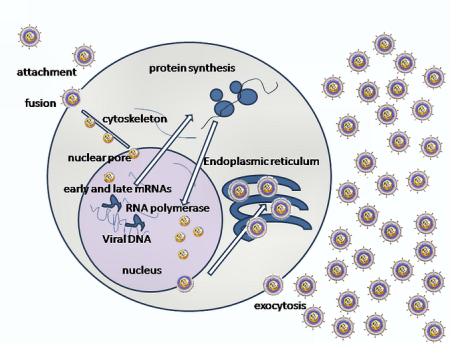

Figure: **Virus replication**: Herpes simplex virus attaches to host cell surface receptors using glycoproteins. Following attachment, the viral envelope fuses with the host cell membrane and the viral capsid gains entry into the cell.

The genome encodes for 11 different glycoproteins, four of which, gB, gC, gD and gH, are involved in viral attachment. Initial interactions occur when viral envelope glycoprotein C (gC) binds to a cell surface particle called heparan sulfate. A second glycoprotein, glycoprotein D (gD), binds specifically to at least one of three known entry receptors. These include herpesvirus entry mediator (HVEM), nectin-1 and 3-O sulfated heparan sulfate. The receptor provides a strong, fixed attachment to the host cell. These interactions bring the membrane surfaces into mutual proximity and allow for other glycoproteins embedded in the viral envelope to interact with other cell surface molecules. Once bound to the HVEM, gD changes its conformation and interacts with viral glycoproteins H (gH) and L (gL), which form a complex. The interaction of these membrane proteins results in the hemifusion state. Afterward, gB interaction with the gH/gL complex creates an entry pore for the viral capsid. Glycoprotein B interacts with glycosaminoglycans on the surface of the host cell.

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9.11E: Replication of Herpes Simplex Virus

Interferons play pivotal roles in shaping the immune responses in mammals.

Learning Objectives

- List the treatments we have to combat viruses

Key Points

- Vaccines prime the body's immune system against specific pathogens, but are not effective for treating an infection.
- Many animal viruses are also important from a human medical perspective. The emergence of the SARS virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. Avian influenza viruses can directly infect humans.
- Immune therapy using immunomodulatory factors, such as interferons, is effective for treatment of hepatitis B and C.
- Immune therapy using immunomodulatory factors, such as interferons, is effective for treatment of hepatitis B and C.

Key Terms

- **foot and mouth disease**: A highly variable and transmissible viral disease. The virus enters the body through inhalation and affects cattle worldwide.
- **interferon**: Any of a group of glycoproteins, produced by the immune system, that prevent viral replication in infected cells.

The study of animal viruses is important from a veterinary viewpoint. Many animal viruses are also important from a human medical perspective. The emergence of the SARS virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. Avian influenza viruses can directly infect humans. In addition research into animal viruses has made an important contribution to our understanding of viruses in general, their replication, molecular biology, evolution, and interaction with the host.

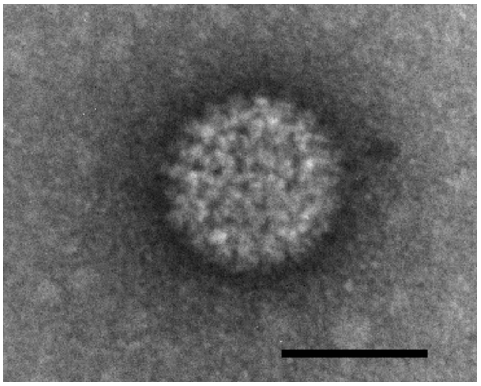

Figure: **TEM of the Bluetongue virus**: Bluetongue virus (BTV), a member of Orbivirus genus within the Reoviridae family causes serious disease in livestock (sheep, goat, cattle).

Rhabdoviruses are a diverse family of single stranded, negative sense RNA viruses that can successfully utilize a myriad of ecological niches, ranging from plants and insects, to fish and mammals. This virus family includes pathogens such as rabies virus, vesicular stomatitis virus, and potato yellow dwarf virus that are of tremendous public health, veterinary, and agricultural significance. Due to the relative simplicity of their genomes and morphology, in recent years rhabdoviruses have become powerful model systems for studying molecular virology.

Foot and mouth disease virus (FMDV) is the prototypic member of the Aphthovirus genus in the Picornaviridae family. This picornavirus is the etiological agent of an acute systemic vesicular disease that affects cattle worldwide, foot-and-mouth disease. FMDV is a highly variable and transmissible virus. It enters the body through inhalation. Soon after infection, the single stranded positive RNA that constitutes the viral genome is efficiently translated using a cap-independent mechanism driven by the internal ribosome entry site element (IRES). This process occurs concomitantly with the inhibition of cellular protein synthesis, caused by the expression of viral proteases. In depth knowledge of the molecular basis of the viral cycle is needed to control viral pathogenesis and disease spreading.

Pestiviruses account for important diseases in animals such as Classical swine fever (CSF) and Bovine viral diarrhea / Mucosal disease (BVD/MD). The molecular biology of pestiviruses shares many similarities and peculiarities with the human hepaciviruses. Genome organization and translation strategy are highly similar for the members of both genera. One hallmark of pestiviruses is their unique strategy to establish persistent infection during pregnancy.

Coronavirus (CoV) genome replication takes place in the cytoplasm in a membrane-protected microenvironment, and starts with the translation of the genome to produce the viral replicase.

The first line of defense against viral infections is usually antiviral vaccines, which prime the body's immune system against specific pathogens. Vaccines traditionally consist of an attenuated (weakened or killed) version of the virus, although many vaccines now target specific immunogenic targets unique to a particular pathogen. Both viral and cellular proteins are required for replication and transcription. CoVs initiate translation by cap-dependent and cap-independent mechanisms. Cell macromolecular synthesis may be controlled after CoV infection by locating some virus proteins in the host cell nucleus. Infection by different coronaviruses cause in the host alteration in the transcription and translation patterns, in the cell cycle, the cytoskeleton, apoptosis and coagulation pathways, inflammation, and immune and stress responses. The balance between genes up- and down-regulated could explain the pathogenesis caused by these viruses.

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, antiviral drugs are usually specific for a particular virus. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

In addition to targeting viral infections directly, some therapeutics work by enhancing the immune responses necessary for viral clearance. One of the best-known of this class of drugs are interferons, which inhibit viral synthesis in infected cells. Interferons (IFNs) play pivotal roles in shaping the immune responses in mammals and are particularly important for the control of viral infections, cell growth, and immune regulation. These proteins rapidly induce an "anti-viral state" in cells that surround infected cells. In order to survive, viruses have evolved multiple strategies to evade the anti-viral effects of IFNs. Elucidating the molecular and cellular biology of the virus-interferon interaction is key to understanding issues such as viral pathogenesis, latency, and the development of novel antivirals.



Figure: **Pediatric polio vaccination in India by a Stop Transmission of Polio (STOP) teams (2002)**: Vaccinations are the best defense against a wide range of viruses, but they are not effective in treating active infections.

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SECTION OVERVIEW

11.10: Immunity and Molecular Signals

Topic hierarchy

11.10A: Clonal Selection and Tolerance

11.10B: Cytokines and Chemokines

11.10C: Superantigens

11.10D: The Complement System

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9.11F: Immunodeficiency

Immunodeficiency occurs when the immune system cannot appropriately respond to infections.

Learning Objectives

- Explain the problems associated with immunodeficiency

Key Points

- If a pathogen is allowed to proliferate to certain levels, the immune system can become overwhelmed; immunodeficiency occurs when the immune system fails to respond sufficiently to a pathogen.
- Immunodeficiency can be caused by many factors, including certain pathogens, malnutrition, chemical exposure, radiation exposure, or even extreme stress.
- HIV is a virus that causes immunodeficiency by infecting helper T cells, causing cytotoxic T cells to destroy them.

Key Terms

- **phagocyte**: a cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria, and waste materials
- **lysis**: the disintegration or destruction of cells
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold to replicate or proliferate to high enough levels that the immune system becomes overwhelmed, leading to immunodeficiency; it may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or, possibly, by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes, elevating an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

HIV/AIDS

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system. The person has a high probability of becoming infected, including from opportunistic infections and tumors that do not usually affect people who have working immune systems.

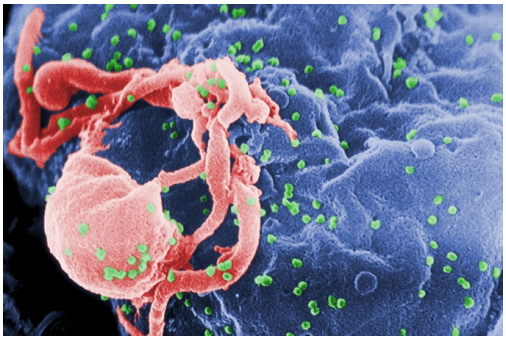

Figure: **Image of HIV: scanning electron micrograph of HIV-1 budding (in green, color added) from cultured lymphocyte**: Multiple round bumps on cell surface represent sites of assembly and budding of HIV. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells, cells that are or will become helper T cells. The acute viremia, or spreading of the virus, is almost invariably associated with activation of CD8+ T cells (which kill HIV-infected cells) and, subsequently, with antibody production. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

Ultimately, HIV causes AIDS by depleting CD4+ T cells (helper T cells). This weakens the immune system, allowing opportunistic infections. T cells are essential to the immune response; without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis (programmed cell death) may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

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9.11G: Double-Stranded DNA Viruses - Pox Viruses

The poxviruses are a family of large, complex, enveloped DNA viruses that infect a variety of vertebrate and invertebrate hosts.

Learning Objectives

- Examine pox viruses for their relevance to human disease and research

Key Points

- The most famous of the poxviruses was smallpox. Smallpox is one of two infectious diseases to have been eradicated, the other being rinderpest, which was declared eradicated in 2011.
- The most abundant and simplest infectious form of the poxvirus particle, the mature virion, consists of the viral DNA genome encased in a proteinaceous core and an outer lipoprotein membrane.
- Poxviruses exhibit a temporally-regulated gene expression program: early, intermediate, and late genes drive DNA replication followed by expression of structural proteins necessary for progeny virion assembly.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **lipoprotein**: Any of a large group of complexes of protein and lipid with many biochemical functions.

The poxviruses are a family of large, complex, enveloped DNA viruses that infect a variety of vertebrate and invertebrate hosts. Poxviruses are of significance both medically and scientifically due to their wide distribution, pathogenicity, and cytoplasmic replicative life cycle. Several prominent members, including variola virus (causative agent of smallpox), molluscum contagiosum virus (cause of a common skin infection of young children and immunosuppressed adults) and monkeypox virus (agent of a smallpox-like disease in parts of Africa), are of considerable concern for public health and biodefense.

The most famous of the poxviruses was smallpox. Smallpox was an infectious disease unique to humans, caused by either of two virus variants, Variola major and Variola minor. The disease is also known by the Latin names Variola or Variola vera, which is a derivative of the Latin varius, meaning “spotted,” or varus, meaning “pimple. ” The term “smallpox” was first used in Britain in the 15th century to distinguish variola from the “great pox” (syphilis). The last naturally occurring case of smallpox (Variola minor) was diagnosed on October 26, 1977. After vaccination campaigns throughout the 19th and 20thcenturies, the World Health Organization (WHO) certified the eradication of smallpox in 1979. Smallpox is one of two infectious diseases to have been eradicated, the other being rinderpest, which was declared eradicated in 2011.

The prototypic and most studied poxvirus, vaccinia virus (VACV), serves as an effective smallpox vaccine, a platform for recombinant vaccines against other pathogens, and an efficient gene expression vector for basic research. Along its approximate 195-kbp double-stranded DNA genome, VACV encodes approximately 200 proteins, ranging in function from viral RNA and DNA synthesis and virion assembly to modulation of host immune defenses.

The most abundant and simplest infectious form of the poxvirus particle, the mature virion (MV), consists of the viral DNA genome encased in a proteinaceous core and an outer lipoprotein membrane with approximately 60 and 25 associated viral proteins, respectively. Following attachment to cell surfaces and fusion with the plasma or endosomal membrane, poxvirus replication is initiated by entry of the viral core into the cytoplasm, where all subsequent steps of the life cycle take place. Poxvirus cores harbor the viral DNA-dependent RNA polymerase and transcription factors necessary for expression of early genes, which constitute nearly half of the viral genome and encode proteins needed for DNA replication and intermediate gene transcription, as well as a large number of immunomodulators.

Poxviruses exhibit a temporally-regulated gene expression program, i.e., expression of early genes encoding DNA replication and intermediate transcription factors triggers the expression of intermediate genes encoding late gene specific transcription factors. Late gene products primarily consist of structural proteins needed for progeny virion assembly, as well as those enzymes destined for incorporation into progeny virions, and used for early gene expression during the next round of infection. Assembly of the MV involves more than 80 viral gene products. In addition, during transit through the cytoplasm, a subset of progeny MVs acquires two additional membrane bilayers, one of which is lost during exocytosis of the particle, to yield the less abundant enveloped virion (EV). Thus, an EV is essentially an MV with an additional membrane in which at least six unique proteins are associated. EVs are

antigenically distinct from MVs and are important for efficient virus dissemination in the infected host and protection against immune defenses. In contrast, MVs are released upon cell lysis and may be important for animal-to-animal transmission.



Figure: **Girl infected with smallpox. Bangladesh, 1973.**: In ordinary type smallpox the bumps are filled with a thick, opaque fluid and often have a depression or dimple in the center. This is a major distinguishing characteristic of smallpox.

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9.11H: Double-Stranded DNA Viruses- Adenoviruses

Learning Objectives

- Define the characteristics of adenoviruses

Adenoviruses are medium-sized (90–100 nm), non-enveloped, icosahedral viruses composed of a nucleocapsid and a linear, double-stranded DNA (dsDNA) genome. There are 57 described serotypes in humans, which are responsible for 5–10% of upper respiratory infections in children, and many infections in adults as well.

Diversity

Viruses of the family *Adenoviridae* infect vertebrates, including humans. Among human-tropic viruses classification can be complex; there are 57 accepted human adenovirus types (HAdV-1 to 57) in seven species (Human adenovirus A to G). Different species/serotypes are associated with different conditions:

- respiratory disease (mainly species HAdV-B and C)
- conjunctivitis (HAdV-B and D)
- gastroenteritis (HAdV-F types 40, 41, HAdV-G type 52)

In addition to human viruses, *Adenoviridae* can be divided into five genera: *Mastadenovirus*, *Aviadenovirus*, *Atadenovirus*, *Siadenovirus*, and *Ichtadenovirus*.

Genome

Structurally, adenoviruses represent the largest non-enveloped viruses. They possess non-segmented dsDNA genomes between 26 and 45 Kbp, significantly larger than other dsDNA viruses. The virion also has unique “spike” or fiber associated with each penton base of the capsid that aids in attachment to the host cell via host cell surface receptors.

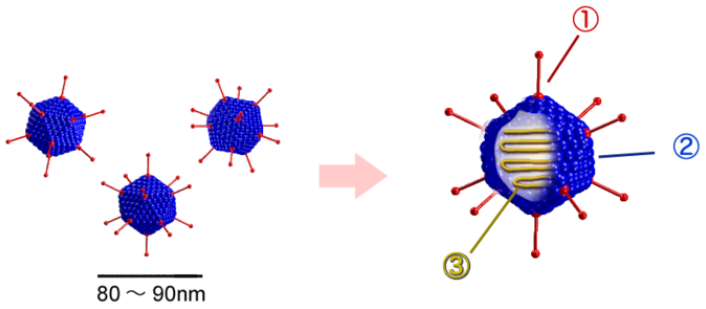

Figure: **Adenovirus Structure**: 1) Penton capsomeres 2) Hexon capsomeres 3) Viral genome (linear dsDNA)

Viral Entry and Replication

Entry of adenoviruses into the host cell involves two sets of interactions between the virus and the host cell. First, entry into the host cell is initiated by the knob domain of the fiber protein binding to a host cell receptor, either CD46 for the group B human adenovirus serotypes, or the coxsackievirus adenovirus receptor for all other serotypes. Next, a specialized motif in the penton base protein interacts with αv integrin, stimulating internalization of the adenovirus via clathrin-coated pits, resulting in entry of the virion into the host cell within an endosome.

Following internalization, the endosome acidifies, which alters virus topology, causing capsid components to disassociate. These changes, as well as the toxic nature of the pentons, result in the release of the virion into the cytoplasm. With the help of cellular microtubules, the virus is transported to the nuclear pore complex, where viral gene expression can occur.

The adenovirus life cycle is separated by the DNA replication process into two phases: an early and a late phase. In both, a primary transcript that is alternatively spliced to generate monocistronic mRNAs compatible with the host’s ribosome is generated, allowing for the products to be translated.

The early genes are responsible for expressing mainly non-structural, regulatory proteins. The goal of these proteins is threefold: to alter the expression of host proteins necessary for DNA synthesis; to activate other viral genes (such as the virus-encoded DNA polymerase); and to avoid premature death of the infected cell by the host-immune defenses (blockage of apoptosis, blockage of interferon activity, and blockage of MHC class I translocation and expression).

The late phase of the adenovirus lifecycle is focused on producing sufficient quantities of structural protein to pack all the genetic material produced by DNA replication. Once the viral components have successfully been replicated, the virus is assembled into its protein shells and released from the cell as a result of virally induced cell lysis.

Transmission

Adenoviruses are unusually stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body and water. Adenoviruses are spread primarily via respiratory droplets; however, they can also be spread by fecal routes.

Humans infected with adenoviruses display a wide range of responses, from no symptoms at all to the severe infections typical of Adenovirus serotype 14. In the past, U.S. military recruits were vaccinated against two serotypes of adenoviruses, with a corresponding decrease in illnesses caused by those serotypes. Although the vaccine is no longer manufactured for civilians, military personnel can receive the vaccine as of 2014.

Infections

Viral transmission occurs primarily through expectorate, but can also be transmitted via contact with infected objects. Most adenovirus infections affect the upper respiratory tract. These often show up as conjunctivitis, tonsillitis, ear infection, or croup. Adenoviruses, types 40 and 41 can also cause gastroenteritis. A combination of conjunctivitis and tonsillitis is particularly common with adenovirus infections. Some children (especially small ones) can develop adenovirus bronchiolitis or pneumonia, both of which can be severe.

Utilization in Treatment of Unrelated Diseases

Adenovirus is used as a vehicle to administer targeted therapy in the form of recombinant DNA or protein. Specific modifications on fiber proteins are used to target Adenovirus to certain cell types; a major effort is made to limit hepatotoxicity and prevent multiple organ failure. Adenovirus dodecahedron serves as a potent delivery platform for foreign antigens to human myeloid dendritic cells (MDC), and is efficiently presented by MDC to M1-specific CD8+ T lymphocytes.

Key Points

- Adenoviruses are medium-sized (90–100 nm), non-enveloped, icosahedral viruses composed of a nucleocapsid and a linear double-stranded DNA (dsDNA) genome.
- There are 57 described serotypes in humans, which are responsible for 5–10% of upper respiratory infections in children, and many infections in adults as well.
- Adenoviruses bind cell surface receptors on host cells, resulting in entry of the virion into the host cell within an endosome.
- The adenovirus life cycle is separated by the DNA replication process into two phases: an early and a late phase. Early genes are responsible for expressing mainly non-structural, regulatory proteins, while late genes produce structural protein necessary for viral replication.

Key Terms

- **endosome**: An endocytic vacuole through which molecules are internalized during endocytosis pass, en route to lysosomes.
- **recombinant DNA**: DNA that has been engineered by splicing together fragments of DNA from multiple species and introduced into the cells of a host.
- **integrin**: Any of many heterodimeric transmembrane proteins that function as receptors in communication between cells.
- **penton**: A pentagonal capsomere of an adenovirus capsid.
- **capsid**: A capsid is the protein shell of a virus.

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9.11I: Retroviruses and Hepadnavirus

Hepadnaviruses, retroviruses, use virally encoded reverse transcriptase to convert RNA into DNA.

Learning Objectives

- Differentiate between retroviruses and hepadnaviruses

Key Points

- Retrovirus RNA serves as a template for reverse transcriptase and is copied into DNA.
- Hepadnaviruses are a family of viruses which can cause liver infections in humans and animals.

Key Terms

- **endogenous**: produced, originating or growing from within
- **episome**: A segment of DNA that can exist and replicate either autonomously in the cytoplasm or as part of achromosome, mainly found in bacteria.

A well-studied family of this class of viruses includes the retroviruses. One defining feature is the use of reverse transcriptase to convert the positive-sense RNA into DNA. Instead of using the RNA for templates of proteins, they use DNA to create the templates, which is spliced into the host genome using integrase. Replication can then commence with the help of the host cell's polymerases. A well-studied example of this includes HIV.

A special variant of retroviruses are endogenous retroviruses, which are integrated into the genome of the host and inherited across generations.

The virus itself stores its nucleic acid in the form of a +mRNA (including the 5'cap and 3'PolyA inside the virion) genome. This then serves as a means of delivery of that genome into cells it targets as an obligate parasite, and constitutes the infection. Once in the host's cell, the RNA strands undergo reverse transcription in the cytoplasm and are integrated into the host's genome, at which point the retroviral DNA is referred to as a provirus. It is difficult to detect the virus until it has infected the host.

In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein. However, retroviruses function differently – their RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translational processes to express the genes carried by the virus. So, the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → protein. This extends the fundamental process identified by Francis Crick, in which the sequence is: DNA → RNA → protein. Retroviruses are proving to be valuable research tools in molecular biology and have been used successfully in gene delivery systems.

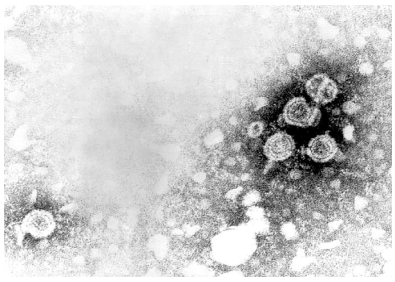

Figure: **Hepatitis B Virus**: TEM micrograph showing hepatitis B virions.

Hepadnaviruses are a family of viruses which can cause liver infections in humans and animals. There are two recognized genera:

- Genus *Orthohepadnavirus* ; type species: *Hepatitis B virus*
- Genus *Avihepadnavirus* ; type species: *Duck hepatitis B virus*

Hepadnaviruses have very small genomes of partially double-stranded, partially single stranded circular DNA. The genome consists of two uneven strands of DNA. One has a negative-sense orientation, and the other, shorter, strand has a positive-sense orientation.Hepadnaviruses replicate through an RNA intermediate (which they transcribe back into cDNA using reverse transcriptase). The reverse transcriptase becomes covalently linked to a short 3- or 4-nucleotide primer. Most hepadnaviruses will only replicate in specific hosts, and this makes experiments using in vitro methods very difficult.

HBV infection is initiated through viral attachment to an unknown cell surface receptor. The virally encoded DNA polymerase acts upon the DNA, leaving it fully double-stranded.

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SECTION OVERVIEW

9. 12: Viruses and Cancer

Topic hierarchy

9.12A: Cancer Viruses

9.12B: DNA Oncogenic Viruses

9.12C: RNA Oncogenic Viruses

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9.12A: Cancer Viruses

Viruses can cause cancer by transforming a normal cell into a malignant cell.

Learning Objectives

- Illustrate how cancer viruses turn normal cells into tumor cells

Key Points

- A direct oncogenic viral mechanism involves either the insertion of additional viral oncogenic genes into the host cell, or the enhancement of already existing oncogenic genes in the genome.
- Tumor viruses come in a variety of forms. Viruses with a DNA genome, such as adenovirus, and viruses with an RNA genome, like the Hepatitis C virus (HCV), can cause cancers. Retroviruses having both DNA and RNA genomes (Human T-lymphotropic virus and hepatitis B virus) can also cause cancers.
- Viruses can become carcinogenic when they integrate into the host cell genome as part of a biological accident, such as polyomaviruses and papillomaviruses.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.
- **transformation**: The alteration of a bacterial cell caused by the transfer of DNA from another, especially if pathogenic.

Worldwide, cancer viruses are estimated to cause 15-20% of all cancers in humans. Most viral infections, however, do not lead to tumor formation; several factors influence the progression from viral infection to cancer development. These factors include host's genetic makeup, mutation occurrence, exposure to cancer causing agents, and immune impairment.

Viruses typically initiate cancer development by suppressing the host's immune system, causing inflammation over a long period of time, or by altering host genes. Cancer cells have characteristics that differ from normal cells, such as acquiring the ability to grow uncontrollably. This can result from having control of their own growth signals, losing sensitivity to anti-growth signals, and losing the ability to undergo apoptosis, or programmed cell death.

Cancer cells don't experience biological aging, and maintain their ability to undergo cell division and growth. Transformation occurs when a virus infects and genetically alters a cell. The infected cell is regulated by the viral genes and has the ability to undergo abnormal new growth. Scientists have been able to discern some commonality among viruses that cause tumors. The tumor viruses or oncoviruses change cells by integrating their genetic material with the host cell's DNA. Unlike the integration seen in prophages, this is a permanent insertion; the genetic material is never removed.

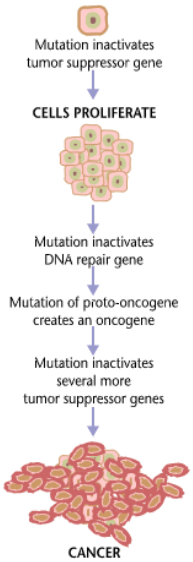

Figure: **Mutations Leading to Increased Cell Division**: Cancer is caused by a series of mutations. Viral infections contribute to the process through genetic alteration.

The insertion mechanism can differ depending on whether the nucleic acid in the virus is DNA or RNA. In DNA viruses, the genetic material can be directly inserted into the host's DNA. RNA viruses must first transcribe RNA to DNA and then insert the genetic material into the host cell's DNA.

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9.12B: DNA Oncogenic Viruses

An estimated 15 percent of all human cancers worldwide may be attributed to viruses.

Learning Objectives

- Outline DNA oncogenic viruses

Key Points

- Both DNA and RNA viruses have been shown to be capable of causing cancer in humans.
- Epstein-Barr virus, human papilloma virus, hepatitis B virus, and human herpes virus-8 are the four DNA viruses that are capable of causing the development of human cancers.
- The presence of viral gene products in tumor cells that require them to maintain their unchecked proliferation, can provide important targets for directed therapies that specifically can distinguish tumor cells from normal cells.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.

There are two classes of cancer viruses: DNA and RNA viruses. Several viruses have been linked to certain types of cancer in humans. These viruses have varying ways of reproduction and represent several different virus families.

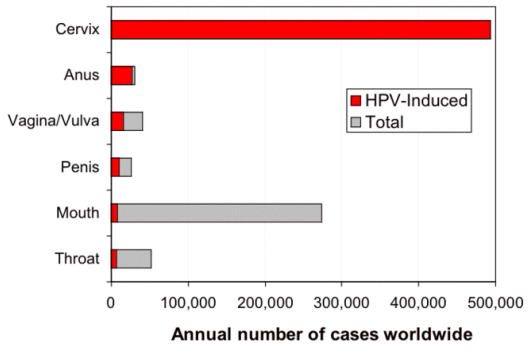

Figure: **Virus Causing Cervical Cancer**: Human papilloma virus is strongly linked to the development of cervical cancer among other types of cancers.

DNA Oncogenic Viruses include the following:

- The Epstein-Barr virus has been linked to Burkitt's lymphoma. This virus infects B cells of the immune system and epithelial cells.
- The hepatitis B virus has been linked to liver cancer in people with chronic infections.
- Human papilloma viruses have been linked to cervical cancer. They also cause warts and benign papillomas.
- Human herpes virus-8 has been linked to the development of Kaposi sarcoma. Kaposi sarcoma causes patches of abnormal tissue to develop in various area of the body including under the skin, in the lining of the mouth, nose, and throat or in other organs.

DNA tumor viruses have two life-styles. In permissive cells, all parts of the viral genome are expressed. This leads to viral replication, cell lysis and cell death. In cells that are non-permissive for replication, viral DNA is usually, but not always, integrated into the cell chromosomes at random sites. Only part of the viral genome is expressed. These are the early control functions of the virus. Viral structural proteins are not made, and no progeny virus is released.

The first DNA tumor viruses to be discovered were rabbit fibroma virus and Shope papilloma virus, both discovered by Richard Shope in the 1930s. Papillomas are benign growths, such as warts, of epithelial cells. They were discovered by making a filtered extract of a tumor from a wild rabbit and injecting the filtrate into another rabbit in which a benign papilloma grew. However, when the filtrate was injected into a domestic rabbit, the result was a carcinoma, a malignant growth. A seminal observation was that it was no longer possible to isolate infectious virus from the malignant growth because the virus had become integrated into the chromosomes of the malignant cells.

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9.12C: RNA Oncogenic Viruses

An estimated 15% of all human cancers worldwide may be attributed to viruses.

Learning Objectives

- Classify the viruses with oncogenic properties

Key Points

- Both DNA and RNA viruses have been shown to be capable of causing cancer in humans.
- Human T lymphotrophic virus type 1 and hepatitis C viruses are the two RNA viruses that contribute to human cancers.
- Hepatitis C virus is an enveloped RNA virus capable of causing acute and chronic hepatitis in humans by infecting liver cells. It is estimated 3% of the world's population are carriers. Chronic infection with hepatitis C virus results in cirrhosis, which in turn can lead to liver cancer.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.
- **hepatocellular**: Of or pertaining to the cells of the liver

There are two classes of cancer viruses: DNA and RNA viruses. Several viruses have been linked to certain types of cancer in humans. These viruses have varying ways of reproduction and represent several different virus families. Specifically, RNA viruses have RNA as their genetic material and can be either single-stranded RNA (ssRNA) or double-stranded (dsRNA). RNA viruses are classified based on the Baltimore classification system and do not take into account viruses with DNA intermediates in their life cycle. Viruses which contain RNA for their genetic material but do include DNA intermediates in their life cycle are called "retroviruses. " There are numerous RNA oncogenic viruses that have been linked to various cancer types. These various oncogenic viruses include:

1. Human T lymphotrophic virus type 1 (HTLV-I), a retrovirus, has been linked to T-cell leukemia. 2. The hepatitis C virus has been linked to liver cancer in people with chronic infections.

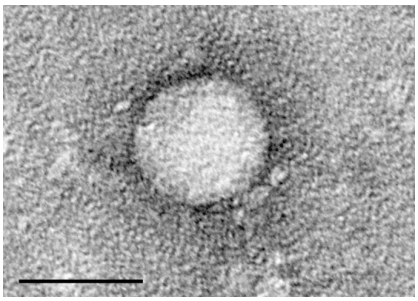

Figure: **Electron micrograph of Hepatitis C**: Hepatitis C viral infections have been linked to the development of liver cancer.

2. Hepatitis viruses includes hepatitis B and hepatitis C have been linked to hepatocellular carcinoma.

3. Human papillomaviruses (HPV) have been linked to cancer of the cervix, anus, penis, vagina/vulva, and some cancers of the head and neck.

4. Kaposi's sarcoma-associated herpesvirus (HHV-8) has been linked to Kaposi's sarcoma and primary effusion lymphoma.

5. Epstein-Barr virus (EBV) has been linked to Burkitt's lymphoma, Hodgkin's lymphoma, post-transplantation lymphoproliferative disease, and nasopharyngeal carcinoma.

RNA Retroviruses

Retroviruses are different from DNA tumor viruses in that their genome is RNA, but they are similar to many DNA tumor viruses in that the genome is integrated into host genome. Since RNA makes up the genome of the mature virus particle, it must be copied to DNA prior to integration into the host cell chromosome. This lifestyle goes against the central dogma of molecular biology in which that DNA is copied into RNA. The outer envelope comes from the host cell plasma membrane. Coat proteins (surface antigens) are encoded by env (envelope) gene and are glycosylated. One primary gene product is made, but this is cleaved so that

there are more than one surface glycoprotein in the mature virus (cleavage is by host enzyme in the Golgi apparatus). The primary protein (before cleavage) is made on ribosomes attached to the endoplasmic reticulum and is a transmembrane (type 1) protein. Inside the membrane is an icosahedral capsid containing proteins encoded by the gag gene (group-specific AntiGen). Gag-encoded proteins also coat the genomic RNA. Again, there is one primary gene product. This is cleaved by a virally-encoded protease (from the pol gene). There are two molecules of genomic RNA per virus particle with a 5′ cap and a 3′ poly A sequence. Thus, the virus is diploid. The RNA is plus sense (same sense as mRNA). About 10 copies of reverse transcriptase are present within the mature virus, these are encoded by the pol gene. Pol gene codes for several functions (again, as with gag and env, a polyprotein is made that is then cut up).

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SECTION OVERVIEW

9. 13: Viral Ecology

Topic hierarchy

9.13A: Emergence of Viral Pathogens

9.13B: Viral Roles in Ecosystems

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11.10A: Clonal Selection and Tolerance

Clonal selection and tolerance select for survival of lymphocytes that will protect the host from foreign antigens.

Learning Objectives

- Describe the importance of central and peripheral tolerance and distinguish between positive and negative clonal selection

Key Points

- Clonal selection occurs after immature lymphocytes express antigen receptors.
- Central tolerance is the mechanism by which newly developing T cells and B cells are rendered non-reactive to self.
- Both developing B cells and T cells are subject to negative selection during a short period after antigen receptors are expressed.
- If, during embryonic development, it encounters its programmed antigen as part of a normal host substance (self), the lymphocyte is somehow destroyed or inactivated. This mechanism removes lymphocytes that can destroy host tissues and thereby creates tolerance for self.

Key Terms

- **lymphocyte**: A type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-lymphocytes, which produce antibodies in the humoral immune response, T-lymphocytes, which participate in the cell-mediated immune response, and the null group, which contains natural killer cells, cytotoxic cells that participate in the innate immune response.
- **antigens**: In immunology, an antigen is a substance that evokes the production of one or more antibodies.
- **T cells**: A lymphocyte, from the thymus, that can recognise specific antigens and can activate or deactivate other immune cells.

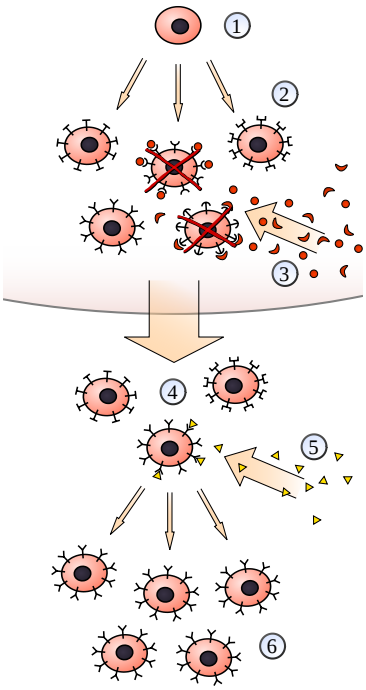

Figure: **Clonal Selection**: clonal selection of the B and T lymphocytes:1. Hematopoietic stem cell 2. Immature lymphocytes with various receptors 3. “Self”-antigens from the body’s own tissues 4. Mature, inactive lymphocytes 5. Foreign antigen 6. Cloned activated lymphocytes.

Central tolerance is the mechanism by which newly developing T cells and B cells are rendered non-reactive to self. The concept of central tolerance was proposed in 1959 as part of a general theory of immunity and tolerance. It was hypothesized that it is the age of the lymphocyte that defines whether an antigen that is encountered will induce tolerance, with immature lymphocytes being tolerance sensitive. The theory that self-tolerance is ‘learned’ during lymphocyte development was a major conceptual contribution to immunology. It was experimentally substantiated in the late 1980’s when tools to analyze lymphocyte development became

available. Central tolerance is distinct from periphery tolerance in that it occurs while cells are still present in the primary lymphoid organs (thymus and bone-marrow), prior to export into the periphery. Peripheral tolerance is generated after the cells reach the periphery. Regulatory T cells can be considered both central tolerance and peripheral tolerance mechanisms, as they can be generated from self (or foreign)-reactive T cells in the thymus during T cell differentiation. However, they exert their immune suppression in the periphery on other self (or foreign)-reactive T cells.

Clonal selection occurs after immature lymphocytes express antigen receptors. The cells with useful receptors are preserved, and many potentially harmful, self antigen-reactive cells are eliminated by processes of selection induced by antigen receptor engagement. The preservation of useful specificities is called positive selection. Positive selection ensures maturation of T cells whose receptors bind weakly to self major histocompatibility complex molecules. Negative selection is the process that eliminates developing lymphocytes whose antigen receptors bind strongly to self antigens present in the lymphoid organs. Both developing B cells and T cells are subject to negative selection during a short period after antigen receptors are expressed. Negative selection of developing lymphocytes is an important mechanism for maintaining central tolerance.

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9.13A: Emergence of Viral Pathogens

Learning Objectives

- Demonstrate the ways a virus can go from benign to pathogenic

Humans or other potential viral hosts are constantly exposed to viruses, yet most viral exposure has no effect. However, many viruses that were once benign later become pathogens through a genetic change, which can occur by different mechanisms. One common evolutionary process whereby viral genes change over time is called genetic drift, where individual bases in the DNA or RNA mutate to other bases. Most of these point mutations are “silent”—they do not change the protein that the gene encodes—but others can confer evolutionary advantages such as resistance to antiviral drugs.

The transformation of viruses from benign to pathogenic occurs via two additional processes more specific to viruses. Viral genomes are constantly mutating, producing new forms of these antigens. If one of these new forms of an antigen is sufficiently different from the old antigen, it will no longer bind to the receptors and viruses with these new antigens can evade immunity to the original strain of the virus. When such a change occurs, people who have had the illness in the past will lose their immunity to the new strain and vaccines against the original virus will also become less effective. Two processes drive the antigens to change: antigenic drift and antigenic shift (antigenic drift being the more common).

Antigenic drift is a mechanism for variation by viruses that involves the accumulation of mutations within the antibody -binding sites so that the resulting viruses cannot be inhibited as well by antibodies against previous strains, making it easier for them to spread throughout a partially immune population. Antigenic drift occurs in both influenza A and influenza B viruses. The rate of antigenic drift is dependent on two characteristics: the duration of the epidemic and the strength of host immunity. A longer epidemic allows for selection pressure to continue over an extended period of time and stronger host immune responses increase selection pressure for the development of novel antigens.

Alternatively, the change can occur by antigenic shift. Antigenic shift is a specific case of reassortment or viral shift that confers a phenotypic change; it is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains. The term is often applied specifically to influenza, as that is the best-known example, but the process also occurs with other viruses, such as the visna virus in sheep. When this happens with influenza viruses, pandemics might result.

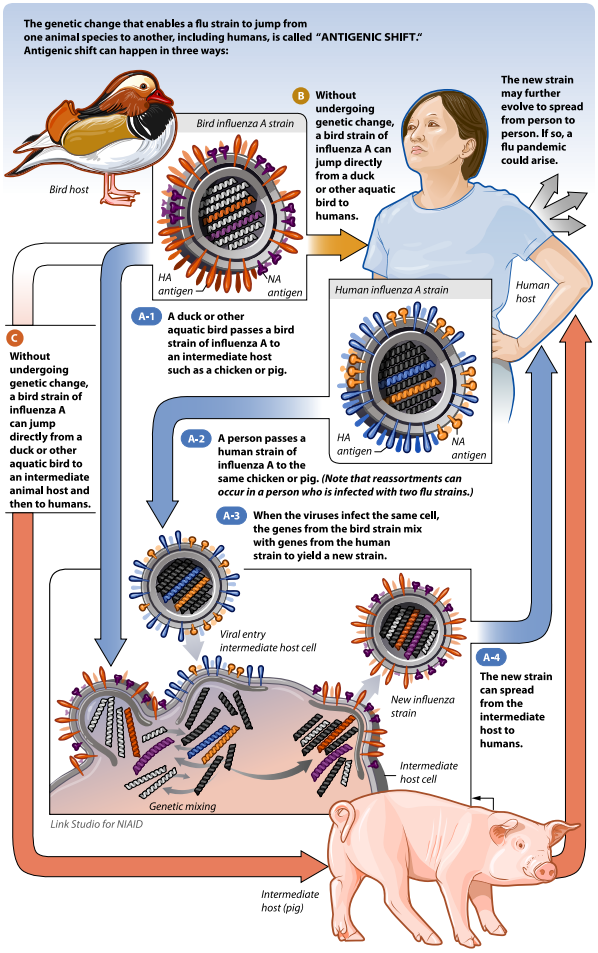

Figure: ***Pathogen emergence by antigenic shift***: *This figure describes in detail how a virus that cannot infect a human can gain the ability to infect a human.*

Antigenic shift occurs only in influenza A because it infects more than just humans. Affected species include other mammals and birds, giving influenza A the opportunity for a major reorganization of surface antigens. Influenza B and C principally infect humans, minimizing the chance that a reassortment will change its phenotype drastically.

For example, if a pig was infected with a human influenza virus and an avian influenza virus at the same time, an antigenic shift could occur, producing a new virus that had most of the genes from the human virus, but a hemagglutinin or neuraminidase from the avian virus. The resulting new virus would likely be able to infect humans and spread from person to person, but it would have surface proteins (hemagglutinin and/or neuraminidase) not previously seen in influenza viruses that infect humans, and therefore most people would have little or no immune protection. If this new virus causes illness in people and can be transmitted easily from person to person, an influenza pandemic can occur. The most recent 2009 H1N1 outbreak was a result of an antigenic shift and reassortment between human, avian, and swine viruses.

Key Points

- For a virus to become pathogenic, genetic changes must occur. These changes occur via mutations, antigenic shift, or antigenic drift.
- Antigenic drift is the natural mutation over time of known strains, thus small changes may cause a harmless virus to become dangerous.
- Antigenic shift is a specific case of reassortment or viral shift that confers a phenotypic change. It is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype that can be more pathogenic than the original strains.
- Antigenic shift is a major driving force behind viruses inhabiting new niches and is responsible for some of the more aggressive human viruses.

Key Terms

- **antigenic shift**: A specific case of reassortment or viral shift that confers a phenotypic change; it is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains.
- **antigenic drift**: A mechanism for variation by viruses that involves the accumulation of mutations within the antibody-binding sites so that the resulting viruses cannot be inhibited as well by antibodies against previous strains, making it easier for them to spread throughout a partially immune population.

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9.13B: Viral Roles in Ecosystems

Learning Objectives

- Show the roles viruses play on ecosystems

Metagenomics is a relatively recent field of study that tries to understand the diversity—especially microbial—of the world around us. Through these studies it is now known that the number of viral particles and number of different viral species in almost every environment on Earth is immense. It is largely believed that viruses by species are the most numerous of any biological entity on earth. This is typified by the role of viruses in marine ecology. A teaspoon of seawater contains about one million viruses.

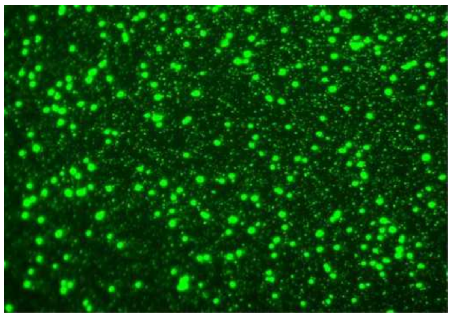

Figure: ***Viral diversity in seawater****: The large green dots are bacteria while the smaller green dots are viral particles. This represents a fraction of the viral diversity seen in teaspoon of marine water.*

Viruses are essential to the regulation of saltwater and freshwater ecosystems. Most of these viruses are bacteriophages, which are harmless to plants and animals. They infect and destroy the bacteria in aquatic microbial communities, comprising the most important mechanism of recycling carbon in the marine environment. The organic molecules released from the bacterial cells by the viruses stimulate fresh bacterial and algal growth.

Microorganisms constitute more than 90% of the biomass in the sea. It is estimated that viruses kill approximately 20% of this biomass each day, and that there are 15 times as many viruses in the oceans as there are bacteria and archaea. Viruses are the main agents responsible for the rapid destruction of harmful algal blooms, which often kill other marine life. The number of viruses in the oceans decreases further offshore and deeper into the water, where there are fewer host organisms. The effects of marine viruses are far-reaching; by increasing the amount of photosynthesis in the oceans, viruses are indirectly responsible for reducing the amount of carbon dioxide in the atmosphere by approximately 3 gigatonnes of carbon per year. Like any organism, marine mammals are susceptible to viral infections. In 1988 and 2002, thousands of harbor seals were killed in Europe by the phocine distemper virus. Many other viruses, including caliciviruses, herpesviruses, adenoviruses, and parvoviruses, circulate in marine mammal populations.

As mentioned, marine viruses are mostly bacteriophages, or phages. Phages are obligate intracellular parasites, meaning that they are able to reproduce only while infecting bacteria. Phages therefore are found only within environments that contain bacteria. Most environments contain bacteria, including our own bodies (called normal flora). Often these bacteria are found in large numbers. As a consequence, phages are found almost everywhere. As a rule of thumb, many phage biologists expect that phage population densities will exceed bacterial densities by a ratio of 10:1 or more (VBR or virus-to-bacterium ratio).

Estimates of bacterial numbers on Earth reach approximately 10^{30}; consequently, there is an expectation that 10^{31} or more individual virus (mostly phage) particles exist, making phages the most numerous category of “organisms” on our planet. Bacteria (along with archaea) appear to be highly diverse and there are possibly millions of species. Phage-ecological interactions therefore are quantitatively vast, with huge numbers of interactions. Phage-ecological interactions are also qualitatively diverse: there are huge numbers of environment types, bacterial-host types, and also individual phage types.

Key Points

- The diversity and numbers of different viruses is incredible.
- In the world’s oceans, 90% of the biomass is microbial, with viruses turning over 20% of that daily. Without the turnover of biomass driven by viruses, many sources of food would not be present for other organisms.
- As bacteria are incredibly diverse, then the viruses that infect them, phages, are even more diverse. As bacteria inhabit almost every niche of the earth, so do viruses.

Key Terms

- **ecological**: Relating to ecology, the interrelationships of organisms and their environment.
- **metagenomics**: The study of genomes recovered from environmental samples; especially the differentiation of genomes from multiple organisms or individuals, either in a symbiotic relationship, or at a crime scene.
- **intracellular**: Inside or within a cell.

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Glossary

Anaplerotic reactions | Chemical reactions that form intermediates of a metabolic pathway.

citric acid cycle | The citric acid cycle (CAC) – also known as the TCA cycle (tricarboxylic acid cycle) or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other reactions. [Wikipedia]

FISH | Fluorescence in situ hybridization is a cytogenetic technique used to detect and localize the specific DNA or RNA sequences. [boundless]

fluorescence | The emission of light (or other electromagnetic radiation) by a material when stimulated by the absorption of radiation or of a subatomic particle [boundless]

GABA | Gamma-Aminobutyric acid is the chief inhibitory neurotransmitter in the developmentally mature mammalian central nervous system. Its principal role is reducing neuronal excitability throughout the nervous system. [Wikipedia]

GABA shunt | The GABA shunt a closed loop that is involved in the production and conservation of the pool of GABA.

glyoxylate Shunt | The glyoxylate shunt is a two-step metabolic pathway (via isocitrate lyase, aceA and malate synthase, glcB) as an alternative to the citric acid cycle.

hybridize | To combine complementary subunits of multiple biological macromolecules. [boundless]

Krebs cycle | The citric acid cycle (CAC) – also known as the TCA cycle (tricarboxylic acid cycle) or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other reactions. [Wikipedia]

Pyruvate Dehydrogenase | Pyruvate dehydrogenase is an enzyme that catalyzes the reaction of pyruvate and a lipoamide to give the acetylated dihydrolipoamide and carbon dioxide. The conversion requires the coenzyme thiamine pyrophosphate. [Wikipedia]

TCA cycle | The citric acid cycle (CAC) – also known as the TCA cycle (tricarboxylic acid cycle) or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other reactions. [Wikipedia]

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11.10B: Cytokines and Chemokines

Cytokines and chemokines are both small proteins secreted by cells of the immune system.

Learning Objectives

- Summarize the role of cytokines and chemokines

Key Points

- Cytokines and chemokines are important in the production and growth of lymphocytes, and in regulating responses to infection or injury, such as inflammation and wound healing.
- Cytokines are the general category of messenger molecules, while chemokines are a special type of cytokine that directs the migration of white blood cells to infected or damaged tissues.
- A cytokine and a chemokine both use chemical signals to induce changes in other cells, but the latter are specialized to cause cell movement.

Key Terms

- **cytokine**: Any of various small regulatory proteins that regulate the cells of the immune system.
- **chemokine**: Any of various cytokines, produced during inflammation, that organize the leukocytes.
- **chemotaxis**: The movement of a cell or an organism in response to a chemical stimulant.

CYTOKINES

These are small cell-signaling protein molecules that are secreted by numerous cells, and are a category of signaling molecules used extensively in intercellular communication.

Cytokines can be classified as proteins, peptides, or glycoproteins. The term “cytokine” encompasses a large and diverse family of regulators produced throughout the body by cells of diverse embryological origin. The term has also been used to refer to the immunomodulating agents, such as interleukins and interferons.

Biochemists disagree as to which molecules should be termed cytokines and which hormones. As we learn more about each, anatomic and structural distinctions between the two are fading. Classic protein hormones circulate in nanomolar (10^{-9}) concentrations that usually vary by less than one order of magnitude. In contrast, some cytokines (such as IL-6) circulate in picomolar (10^{-12}) concentrations that can increase up to 1,000-fold during trauma or infection.

The widespread distribution of cellular sources for cytokines may be a feature that differentiates them from hormones. Virtually all nucleated cells, but especially endo/epithelial cells and resident macrophages (many near the interface with the external environment), are potent producers of IL-1, IL-6, and TNF-alpha. In contrast, classic hormones, such as insulin, are secreted from discrete glands (e.g., the pancreas).

As of 2008, the current terminology refers to cytokines as immunomodulating agents.

CHEMOKINES

These are a family of small cytokines, or proteins secreted by cells. Their name is derived from their ability to induce directed chemotaxis in nearby responsive cells; they are chemotactic cytokines.

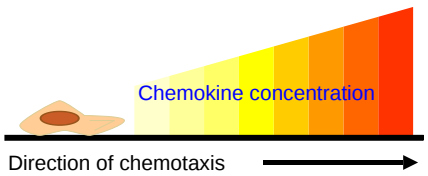

Figure: **Chemotaxis**: Effect of chemokine concentration gradient on chemotaxis direction.

Proteins are classified as chemokines according to shared structural characteristics, such as small size (they are all approximately 8-10 kilodaltons in size), and the presence of four cysteine residues in conserved locations that are key to forming their 3-dimensional shape. However, these proteins have historically been known under several other names including the SIS family of cytokines, SIG family of cytokines, SCY family of cytokines, Platelet factor-4 superfamily or intercrines.

Some chemokines are considered pro-inflammatory and can be induced during an immune response to recruit cells of the immune system to a site of infection, while others are considered homeostatic and are involved in controlling the migration of cells during normal processes of tissue maintenance or development.

Chemokines are found in all vertebrates, some viruses and some bacteria, but none have been described for other invertebrates. These proteins exert their biological effects by interacting with G protein-linked transmembrane receptors called chemokine receptors, that are selectively found on the surfaces of their target cells.

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11.10C: Superantigens

Superantigens are a class of antigens that cause activation of T-cells and massive cytokine release.

Learning Objectives

- Describe the mechanism of action for superantigens and the effects

Key Points

- Superantigens (SAgs) are microbial products that have the ability to promote massive activation of immune cells, leading to the release of inflammatory mediators that can ultimately result in hypotension, shock, organ failure, and death.
- They achieve this by simultaneously binding and activating major histocompatibility complex class II molecules on antigen - presenting cells and T-cell receptors on T lymphocytes bearing susceptible Vβ regions.
- The resulting Th1 response may divert the immune system from effective microbial clearance and/or result in the cytokine - mediated suppression and deletion of activated T cells.

Key Terms

- **interferon**: Any of a group of glycoproteins, produced by the immune system, that prevent viral replication in infected cells.
- **Kawasaki disease**: A disease in which the medium-sized blood vessels throughout the body become inflamed. Symptoms include fever, lymphadenopathy, and elevated platelet count.
- **superantigen**: an antigen, which has a powerful interaction with T-lymphocytes

Superantigens (SAgs) are proteins that cause the T-cells of the immune system to over-react to infection. They are produced by certain infectious bacteria and viruses. The immune system over-reaction to the antigen causes a group of diseases that manifest in fever and shock, such as food poisoning, toxic shock syndrome, and Kawasaki disease. Common bacterial species that may use a superantigen as part of their virulence strategy are staphylococci and streptococci.

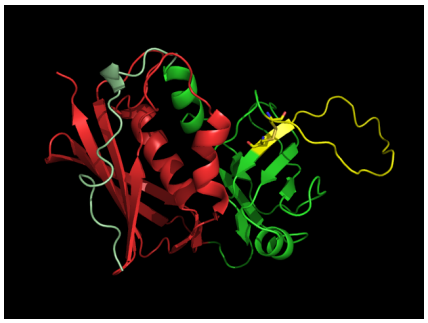

Figure: **A Superantigen**: Structure of a typical bacterial superantigen.

These bacteria usually live harmlessly on the body, but can cause infections in certain circumstances. The superantigens of each species are, like antigens, molecules the immune system recognizes as being foreign. Superantigens cause symptoms of illness by tricking the T-cells of the immune system into over-reacting to these molecules. Parts of a bacterium or a virus are usually recognized by the macrophage cells of the immune system. The macrophage ingests the foreign invaders and breaks them down. Then the macrophage takes parts of the broken-down invader or other molecules that it ingested and posts the fragments on the outside of the cell using a major histocompatibility complex (MHC) to hold the fragment.

The large number of activated T-cells generates a massive immune response which is not specific to any particular epitope on the SAg. This undermines one of the fundamental strengths of the adaptive immune system, that is, its ability to target antigens with high specificity. More importantly, the large number of activated T-cells secretes large amounts of cytokines, the most important of which is Interferon gamma. This excess amount of IFN-gamma is in turn what activates the macrophages.

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11.10D: The Complement System

The complement system helps antibodies and phagocytic cells clear pathogens from an organism.

Learning Objectives

- Describe the function of the complement system

Key Points

- The complement system has originally been identified as the part of the immune system called the innate immune system.
- The complement system can also be recruited and brought into action by the adaptive immune system.
- The three biochemical pathways that activate the complement system are the classical complement pathway, the alternative complement pathway, and the lectin pathway.
- The complement system consists of small proteins found in the blood, generally synthesized by the liver, and normally circulating as inactive precursors. When stimulated by a trigger, proteases in the system cleave specific proteins to release cytokines that amplify further cleavages.
- The end-result of this activation cascade is the massive amplification of the response and activation of the cell-killing membrane attack complex.

Key Terms

- **opsonization**: the process of an antigen bound by antibody or complement to attract phagocytic cells.

The Complement System

The serum complement system, which represents a chief component of innate immunity, not only participates in inflammation but also acts to enhance the adaptive immune response. Specific activation of the complement via innate recognition proteins or secreted antibody releases cleavage products that interact with a wide range of cell surface receptors found on myeloid, lymphoid, and stromal cells. This intricate interaction among complement activation products and cell surface receptors provides a basis for the regulation of both B and T cell responses.

The complement system plays a crucial role in the innate defense against common pathogens. Activation of the complement leads to robust and efficient proteolytic cascades, which terminate in opsonization and lysis of the pathogen as well as in the generation of the classical inflammatory response through the production of potent proinflammatory molecules. More recently, however, the role of the complement in the immune response has been expanded due to observations that link complement activation to adaptive immune responses. It is now understood that the complement is a functional bridge between innate and adaptive immune responses that allows an integrated host defense to pathogenic challenges.

Activation of the Complement System

The complement system can be activated through three major pathways: classical, lectin, and alternative. Initiation of the classical pathway occurs when C1q, in complex with C1r and C1s serine proteases (the C1 complex), binds to the Fc region of complement-fixing antibodies (generally $IgG_1$and IgM) attached to pathogenic surfaces. Autocatalytic activation of C1r and C1s in turn cleaves C4 and C2 into larger (C4b, C2a) and smaller (C4a, C2b) fragments. The larger fragments associate to form C4bC2a on pathogenic surfaces, and the complex gains the ability to cleave C3 and is termed the C3 convertase.

Generation of the C3 convertase, which cleaves C3 into the anaphylatoxin C3a and the opsonin C3b, is the point at which all complement activation cascades converge. When C3 is cleaved into C3b, it exposes an internal thioester bond that allows stable covalent binding of C3b to hydroxyl groups on proximate carbohydrates and proteins. This activity underpins the entire complement system by effectively “tagging” microorganisms as foreign, leading to further complement activation on and around the opsonized surface and terminating in the production of anaphylatoxins and assembly of membrane attack complexes.

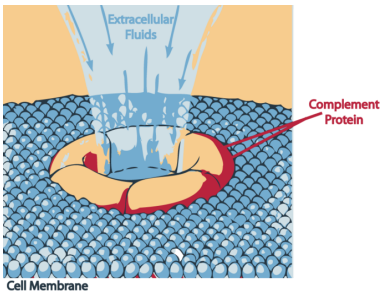

Figure: **Complement death**: A complement protein attacking an invader.

Functions of the Complement System

The functions of the complement system, oposonization, lysis, and generation of the inflammatory response through soluble mediators, are paradigmatic and represent a well-characterized component of an innate host defense. It has become increasingly understood that complement functions in host defense extend beyond innate immune responses. The finding that B lymphocytes bound C3 raised the question as early as in the 1970s as to whether the complement system was involved in adaptive immune responses. Subsequent work demonstrated that depletion of C3 impaired humoral immune responses and provided direct evidence that efficient adaptive responses were contingent on an intact complement system in some cases.

Further study in animals bearing natural complement deficiencies implicated the classical pathway as a crucial mechanism for efficient antigen trapping and retention in lymphoid tissues (e.g., splenic follicles), suggesting that a major function of the complement system was to localize foreign antigens into immune sites important for lymphocytes responses.

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SECTION OVERVIEW

11.11: The Major Histocompatibility Complex (MHC)

Topic hierarchy

11.11A: MHC Polymorphism and Antigen Binding

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11.11A: MHC Polymorphism and Antigen Binding

Learning Objectives

- Explain MHC polymorphism

Major histocompatibility complex (MHC) is a cell-surface molecule encoded by a large gene family in all vertebrates. MHC molecules display a molecular fraction called an epitope and mediate interactions of leukocytes with other leukocytes or body cells. The MHC gene family is divided into three subgroups—class I, class II, and class III. Diversity of antigen presentation, mediated by MHC classes I and II, is attained in multiple ways:

1. The MHC's genetic encoding is polygenic,
2. MHC genes are highly polymorphic and have many variants,
3. Several MHC genes are expressed from both inherited alleles (variants).

MHC gene families are found in all vertebrates, though they vary widely. Chickens have among the smallest known MHC regions (19 genes).

In humans, the MHC region occurs on chromosome 6. Human MHC class I and II are also called human leukocyte antigen (HLA). To clarify the usage, some of the biomedical literature uses HLA to refer specifically to the HLA protein molecules and reserves MHC for the region of the genome that encodes for this molecule, but this is not a consistent convention.

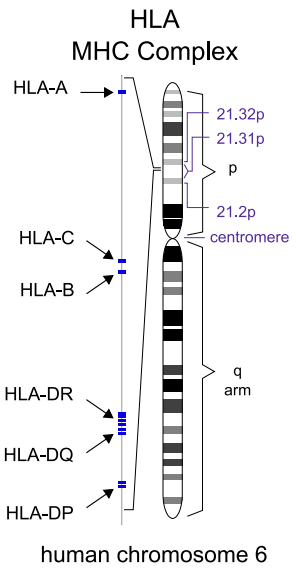

Figure: ***HLA MHC complex****: The human leukocyte antigen (HLA) system is the name of the major histocompatibility complex (MHC) in humans. The super locus contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6, encodes cell-surface antigen-presenting proteins and has many other functions.*

The most intensely-studied HLA genes are the nine so-called classical MHC genes: HLA-A, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1. In humans, the MHC is divided into three regions: classes I, II, and III. The A, B, C, E, F, and G genes belong to MHC class I, whereas the six D genes belong to class II. MHC genes are expressed in co-dominant fashion. This means that the alleles inherited from both progenitors are expressed in an equivalent way. As there are 3 Class-I genes, named in humans HLA-A, HLA-B and HLA-C, and as each person inherits a set of genes from each progenitor, that means that any cell in an individual can express 6 different types of MHC-I molecules.

In the Class-II locus, each person inherits a couple of genes HLA-DP (DPA1 and DPA2, which encode α and β chains), a couple of genes HLA-DQ (DQA1 and DQA2, for α and β chains), one gene HLA-DRα (DRA1) and one or two genes HLA-DRβ (DRB1 and DRB3, -4 o -5). That means that one heterozygous individual can inherit 6 or 8 Class-II alleles, three or four from each progenitor.

The set of alleles that is present in each chromosome is called MHC haplotype. In humans, each HLA allele is named with a number. Each heterozygous individual will have two MHC haplotypes, one in each chromosome (one of paternal origin and the

other of maternal origin).

The MHC genes are highly polymorphic; this means that there are many different alleles in the different individuals inside a population. The polymorphism is so high that in a mixed population (non-endogamic) there are not two individuals with exactly the same set of MHC genes and molecules, with the exception of identical twins.

The polymorphic regions in each allele are located in the region for peptide contact, which is going to be displayed to the lymphocyte. For this reason, the contact region for each allele of MHC molecule is highly variable, as the polymorphic residues of the MHC will create specific clefts in which only certain types of residues of the peptide can enter. This imposes a very specific link between the MHC molecule and the peptide, and it implies that each MHC variant will be able to bind specifically only those peptides that are able to properly enter in the cleft of the MHC molecule, which is variable for each allele. In this way, the MHC molecules have a broad specificity, because they can bind many, but not all, types of possible peptides.

The evolution of the MHC polymorphism ensures that a population will not succumb to a new pathogen or a mutated one, because at least some individuals will be able to develop an adequate immune response to win over the pathogen. The variations in the MHC molecules (responsible for the polymorphism) are the result of the inheritance of different MHC molecules, and they are not induced by recombination, as it is the case for the antigen receptors.

Because of the high levels of allelic diversity found within its genes, MHC has also attracted the attention of many evolutionary biologists.

Key Points

- Diversity of antigen presentation, mediated by MHC classes I and II, is attained in three ways: (1) the MHC's genetic encoding is polygenic, (2) MHC genes are highly polymorphic and have many variants, (3) several MHC genes are expressed from both inherited alleles.
- Human MHC class I and II are also called human leukocyte antigen (HLA).
- The MHC genes are highly polymorphic; this means that there are many different alleles in the different individuals inside a population.
- The evolution of the MHC polymorphism ensures that a population will not succumb to a new pathogen or a mutated one, because at least some individuals will be able to develop an adequate immune response to win over the pathogen.

Key Terms

- **allele**: One of a number of alternative forms of the same gene occupying a given position on a chromosome.
- **epitope**: That part of a biomolecule (such as a protein) that is the target of an immune response.
- **polygenic**: Having an infinite number of derivatives at a point (otherwise it is monogenic).

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SECTION OVERVIEW

11.12: Classifying Immunities

Topic hierarchy

11.12A: Natural Active Immunity

11.12B: Natural Passive Immunity

11.12C: Artificial Immunity

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11.12A: Natural Active Immunity

Naturally acquired active immunity occurs when a person is exposed to a live pathogen, develops the disease, and then develops immunity.

Learning Objectives

- Compare and contrast: active natural and active artifical immunity

Key Points

- Once a microbe penetrates the body's skin, mucous membranes, or other primary defenses, it interacts with the immune system.
- Active immunization entails the introduction of a foreign molecule into the body, which causes the development of an immnune response via activation of the T cells and B cells.
- The principle behind immunization is to introduce an antigen, derived from a disease-causing organism, that stimulates the immune system to develop protective immunity against that organism, but which does not itself cause the pathogenic effects of that organism.

Key Terms

- **immunity**: the state of being insusceptible to a specific thing.
- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.

Immunity is the state of protection against infectious disease conferred either through an immune response generated by immunization or previous infection, or by other non-immunological factors. There are two ways to acquire active resistance against invading microbes: active natural and active artificial.



Figure: **Typhoid vaccination**: Immunization (commonly referred to as vaccination) is the deliberate induction of an immune response, and represents the single most effective manipulation of the immune system that scientists have developed.

Naturally acquired active immunity occurs when the person is exposed to a live pathogen, develops the disease, and becomes immune as a result of the primary immune response. Once a microbe penetrates the body's skin, mucous membranes, or other primary defenses, it interacts with the immune system. B-cells in the body produce antibodies that help to fight against the invading microbes. The adaptive immune response generated against the pathogen takes days or weeks to develop but may be long-lasting, or even lifelong. Wild infection, for example with hepatitis A virus (HAV) and subsequent recovery, gives rise to a natural active immune response usually leading to lifelong protection.

In a similar manner, administration of two doses of hepatitis A vaccine generates an acquired active immune response leading to long-lasting (possibly lifelong) protection. Immunization (commonly referred to as vaccination) is the deliberate induction of an immune response, and represents the single most effective manipulation of the immune system that scientists have developed. Immunizations are successful because they utilize the immune system's natural specificity as well as its inducibility. The principle behind immunization is to introduce an antigen, derived from a disease-causing organism, that stimulates the immune system to develop protective immunity against that organism, but which does not itself cause the pathogenic effects of that organism.

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11.12B: Natural Passive Immunity

Naturally acquired passive immunity occurs during pregnancy, when antibodies are passed from the maternal blood into the fetal bloodstream.

Learning Objectives

- Outline the various ways to obtain passive immunity

Key Points

- Immunity is transferred through the placenta in the form of antibodies, mainly IgG and IgA.
- Natural passive immunity can also be transferred through breast milk.
- Natural passive immunity is short-lived after the birth of the child.

Key Terms

- **IgG**: immunoglobulin G is an antibody isotype.
- **IgA**: immunoglobulin A is an antibody isotype.
- **passive immunity**: the translocation of active humoral immunity from one individual to another in the form of custom-made antibodies.

Immunity is the state of protection against infectious disease conferred either through an immune response generated by immunization or previous infection, or by other non-immunological factors. There are two ways to acquire passive resistance against disease: passive natural and passive artificial. Naturally acquired passive immunity occurs during pregnancy, in which certain antibodies are passed from the maternal blood into the fetal bloodstream in the form of IgG. Antibodies are transferred from one person to another through natural means such as in prenatal and postnatal relationships between mother and child. Some antibodies can cross the placenta and enter the fetal blood. This provides some protection for the child for a short time after birth, but eventually these deteriorate and the infant must rely on its own immune system. Antibodies may also be transferred through breast milk. The transfered IgG from mother to fetus during pregnancy generally lasts 4 to 6 months after birth. The immune responses reach full strength at about age 5.

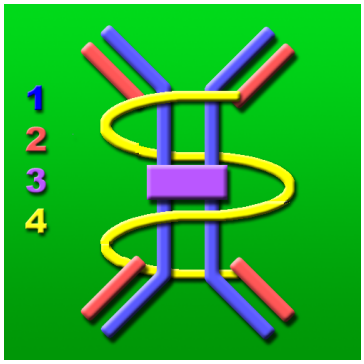

Figure: **IgA antibody**: The dimeric IgA molecule.1 H-chain2 L-chain3 J-chain4 secretory component. IgA antibodies are transferred from mother to child in colostrum and milk and confer passive immunity.

Passive immunity can also be in the form of IgA and IgG found in human colostrum and milk of babies who are nursed. In addition to the IgA and IgG, human milk also contains: oligosaccharides and mucins that adhere to bacteria and viruses to interfere with their attachment to host cells; lactoferrin to bind iron and make it unavailable to most bacteria; B_{12} binding protein to deprive bacteria of needed vitamin $B_{12;}$ bifidus factor that promotes the growth of Lactobacillus bifidus, normal flora in the gastrointestinal tract of infants that crowds out harmful bacteria; fibronectin that increases the antimicrobial activity of macrophages and helps repair tissue damage from infection in the gastrointestinal tract; gamma-interferon, a cytokine that enhances the activity of certain immune cells; hormones and growth factors that stimulate the baby's gastrointestinal tract to mature faster and be less susceptible to infection; and lysozyme to break down peptidoglycan in bacterial cell walls.

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11.12C: Artificial Immunity

Artificial immunity is a mean by which the body is given immunity to a disease by intentional exposure to small quantities of it.

Learning Objectives

- Describe artificially acquired immunity and how it is obtained

Key Points

- The most common form of artificial immunity is classified as active and comes in the form of vaccinations, typically given to children and young adults.
- The passive form of artificial immunity involves introducing an antibody into the system once a person has already been infected with a disease, ultimately relieving the present symptoms of the sickness and preventing re-occurrence.
- Once the body has successfully rid itself of a disease caused by a certain pathogen, a second infection with the same pathogen would prove harmless.

Key Terms

- **gamma globulin**: a class of proteins in the blood, identified by their position after serum protein electrophoresis, such as antibodies
- **anaphylactic shock**: A severe and rapid systemic allergic reaction to an allergen, constricting the trachea and preventing breathing.
- **herd immunity**: the protection given to a community against an epidemic of a contagious disease when a sufficient number of the population are immunised or otherwise develop immunity to it

Immunity is the state of protection against infectious disease conferred either through an immune response generated by immunization or by previous infection or other non-immunological factors.

Artificial immunity can be active or passive.

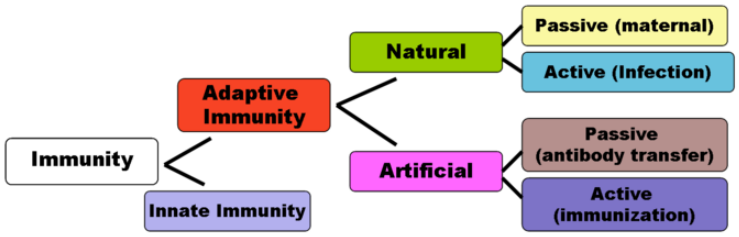

Figure: **Immunity**: Natural immunity occurs through contact with a disease causing agent, when the contact was not deliberate, where as artificial immunity develops only through deliberate actions of exposure. Both natural and artificial immunity can be further subdivided, depending on the amount of time the protection lasts. Passive immunity is short lived, and usually lasts only a few months, whereas protection via active immunity lasts much longer, and is sometimes life-long.

Artificially-acquired passive immunity is an immediate, but short-term immunization provided by the injection of antibodies, such as gamma globulin, that are not produced by the recipient's cells. These antibodies are developed in another individual or animal and then injected into another individual. Antiserum is the general term used for preparations that contains antibodies.

Artificial active immunization is where the microbe, or parts of it, are injected into the person before they are able to take it in naturally. If whole microbes are used, they are pre-treated, attenuated vaccines. This vaccine stimulates a primary response against the antigen in the recipient without causing symptoms of the disease.

Artificial passive immunization is normally administered by injection and is used if there has been a recent outbreak of a particular disease or as an emergency treatment for toxicity, as in for tetanus. The antibodies can be produced in animals, called " serum therapy," although there is a high chance of anaphylactic shock because of immunity against animal serum itself. Thus, humanized antibodies produced in vitro by cell culture are used instead if available.

The first record of artificial immunity was in relation to a disease known as smallpox. Individuals were exposed to a minor strain of smallpox in a controlled environment. Once their bodies built up a natural immunity or resistance to the weakened strain of smallpox, they became much less likely to become infected with the more deadly strains of the disease. In essence, patients were

given the disease in order to help fight it later in life. Although this method was an effective one, the scientists of the time had no real scientific knowledge of why it worked.

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Thumbnail: Multiple plantar warts have grown on this toe.

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SECTION OVERVIEW

12.1: Immunization

Topic hierarchy

12.1A: Passive Immunization

12.1B: Vaccination

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12.1A: Passive Immunization

Learning Objectives

- Describe how artificial and natural passive immunity function to provide antibody protection against microorganisms

There are two types of passive immunity: artificial and natural. Artificial passive immunity is achieved by infusion of serum or plasma containing high concentrations of antibody. This form of passive immunity provides immediate antibody protection against microorganisms such as hepatitis A by administering preformed antibodies. These antibodies have been produced by another person or animal that has been actively immunized, but the ultimate recipient has not produced them. The recipient will only temporarily benefit from passive immunity for as long as the antibodies persist in their circulation.This type of immunity is short acting, and is typically seen in cases where a patient needs immediate protection from a foreign body and cannot form antibodies quickly enough independently.

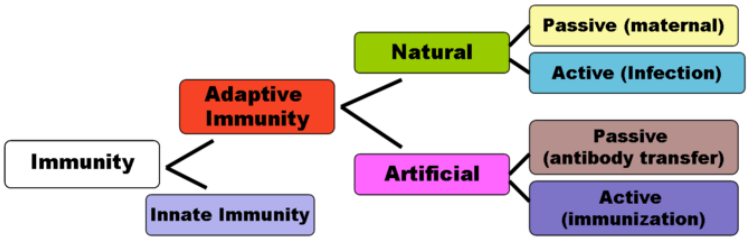

Figure: ***Immunity****: Natural immunity occurs through contact with a disease causing agent, when the contact was not deliberate, where as artificial immunity develops only through deliberate actions of exposure. Both natural and artificial immunity can be further subdivided, depending on the amount of time the protection lasts. Passive immunity is short lived, and usually lasts only a few months, whereas protection via active immunity lasts much longer, and is sometimes life-long.*

Passive immunity can also be acquired naturally by the fetus due to the transfer of antibodies by the maternal circulation in utero through the placenta around the third month of gestation. Immunity in newborn babies is only temporary and starts to decrease after the first few weeks, or months. Breast milk also contains antibodies, which means that babies who are breastfed have passive immunity for longer periods of time. The thick, yellowish milk (colostrum) that is produced during the first few days after birth is particularly rich in antibodies. For the newborn to have lasting protection, active immunity must be received. The first immunisation, given when a baby is two months old, includes whooping cough and Hib (haemophilus influenza type b) because immunity to these diseases decreases the fastest. Passive immunity to measles, mumps and rubella (MMR) usually lasts for about a year, which is why the MMR is given just after the baby's first birthday.

Key Points

- Passive immunization provides humoral immunity.
- Artificial passive immunization is the injection of preformed antibody solution when a patient is incapable of producing antibodies fast enough to combat a disease.
- Natural passive immunization is the transfer of antibodies through the placenta of a pregnant woman to the fetus. Immunity lasts for a couple of months after the baby is born, after which active immunization is required.

Key Terms

- **in utero**: Occurring or residing within the uterus or womb; unborn.

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12.1B: Vaccination

Vaccination is a proven way to prevent and even eradicate widespread outbreaks of life-threatening infectious diseases.

Learning Objectives

- Describe how active immunity to diseases can be acquired by natural exposure or by vaccination

Key Points

- Immunization is the administration of antigenic solution, usually orally or via injection, to protect against infectious bacterial and viral diseases.
- Vaccinations are usually given at specific ages and dates as per the recommended schedule provided by The Center for Disease Control.
- Vaccines stimulate the body to produce antibodies without manifesting clinical signs and symptoms of the disease in immunocompetent hosts.

Key Terms

- **toxoids**: bacterial toxins whose toxicity has been inactivated or suppressed.
- **immunity**: the state of being insusceptible to a specific thing.
- **immunocompetent**: Having a functioning immune system.

Active immunity to diseases can be acquired by natural exposure (in response to actually contracting an infectious disease) or it may be acquired intentionally, via the administration of an antigen, commonly known as vaccination.



Figure: **Vaccination:**: a child receiving an oral polio vaccine.

Vaccination has proven to be an effective way to stimulate the human body's natural ability to produce antibodies, without contracting the disease and suffering any of its effects. This is also known as 'acquired' resistance.

The various antigenic materials used in these vaccinations (or immunization) may be of animal or plant origin. Some vaccinations are composed of live suspensions of weak or attenuated cells or viruses, deadened cells or viruses, or extracted bacterial products such as the *toxoids* used to immunize against diphtheria and tetanus.

Vaccinations are developed to stimulate the body's production of antibodies without the manifestation of clinical signs and symptoms of the disease in *immunocompetent* hosts. Moreover, active immunization should cause permanent antigenic memory or lifelong immunity.

Vaccinations are usually given at specific ages and dates according to the recommended schedule provided by The Center for Disease Control. Sometimes booster vaccinations are needed to provide additional *immunity* in certain individuals and in certain cases.

Once your immune system has been trained to resist a disease, you are said to be immune to it. Before vaccines were developed, the only way to acquire immunity to a disease was to actually get it and, with luck, survive it. Even today, the risk of contracting some of these infectious diseases, like measles and chicken pox, can have devastating, long-term complications, like blindness.

Despite some of the various controversies surrounding vaccines over the years, the tiny proportion of risk is far outweighed by the numerous benefits. Certain infectious diseases, such as Smallpox, have been completely eradicated. Global mass vaccination drives have met with enormous success in reducing the incidence of many diseases.

Another consideration is that the newer vaccination programs also protect older age groups. By these vaccinated children not contracting these diseases, their parents, grandparents, friends and relatives (not vaccinated against these diseases themselves) will also be protected.

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12.1C: Development of New Vaccines

New vaccines are being developed to control recent infectious disease epidemics and cancers.

Learning Objectives

- Describe how new vaccines are being developed to help eradicate several infectious global diseases

Key Points

- The World Health Organization (WHO) oversees the development and distribution of vaccines for underdeveloped countries.
- Vaccines for rotavirus diarrhea, pneumococcal disease, and meningococcal infections have been licensed and are approved for development.
- Vaccines for cancer treatment are gaining traction and are based on training the body to recognize cancer cells as foreign.

Key Terms

- **vaccine**: a substance given to stimulate the body's production of antibodies and provide immunity against a disease, prepared from the agent that causes the disease, or a synthetic substitute.
- **immunization**: the process by which an individual is exposed to a material that is designed to prime his or her immune system against that material.

National Immunization Programs

The implementation of large-scale, comprehensive national immunization programs, and the considerable successes that were achieved in the eradication of smallpox and the reduction of polio, measles, pertussis, tetanus, and meningitis, were among the most notable achievements of the 20th century. Even in the poorest countries, immunizations have been able to achieve significant progress in disease control. There is good reason to expect that these advances will be sustained and will progress even further in the 21stcentury.

Vaccines for Infectious Diseases

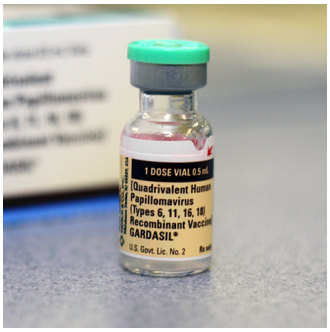

Figure: **Human papillomavirus vaccine**: Gardasil is a human papillomavirus vaccine on the market and it protects against HPV-16 and HPV-18 which cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers.

A number of new vaccines with major potential for controlling infectious diseases have just been licensed or are at advanced stages of development. Among the illnesses targeted are rotavirus diarrhea, pneumococcal disease, and cervical cancer (as caused by human papillomavirus), which together kill more than a million people each year, most of them in developing countries.

In addition to these efforts against global diseases, progress is being made on a vaccine for the regional menace posed by meningococcal meningitis serogroup A, which causes frequent epidemics and high death rates and disability in African countries south of the Sahara. Continuing intensive efforts are under way to develop effective vaccines for AIDS, malaria, tuberculosis, dengue, leishmaniasis, and enteric diseases, among others and to adapt new technologies to improve formulation and delivery. The World Health Organization (WHO) facilitates the development of vaccines against infectious diseases of major public health importance, helps improve existing immunization technologies, and ensures that these advances are made available to the people who need them the most.

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12.1D: Vaccine Safety

Vaccines carry risks, ranging from rashes or tenderness at the site of injection to fever-associated seizures.

Learning Objectives

- Describe the possible side effects of vaccine administration

Key Points

- Vaccines can cause side effects in immunocompromised people, and allergic reactions due to the ingredients used to make them stable.
- Side effects from vaccines are rare and most reported ailments after vaccination have not been proven to be caused by vaccination (e.g. autism, asthma).
- Researchers continue to ameliorate vaccines composition making them safer and effective.

Key Terms

- **convulsion**: An intense, paroxysmal, involuntary muscular contraction.
- **subunit vaccine**: a vaccine that presents an antigen to the immune system without introducing viral particles, whole or otherwise
- **limpness**: Property of being limp.

Vaccines are biological products with biological effects. Vaccines are made with a variety of ingredients including antigens, stabilizers, adjuvants, and preservatives; they may also contain residual by-products from the production process. These might be the cause of allergic reactions and side effects.

Vaccines carry risks, ranging from rashes or tenderness at the site of injection to fever-associated seizures called febrile convulsions and dangerous infections in those with compromised immune systems. Technological advances have made modern vaccines purer and safer than their historical counterparts. Most developed countries have switched to the inactivated polio vaccine and stopped using whole-cell pertussis (whooping cough) vaccines, which are made from killed bacteria and cause relatively high rates of arm swelling, febrile convulsions and periods of limpness or unresponsiveness.

Researchers have long known that some individuals are more susceptible to vaccine risks than others. Immunocompromised individuals have generally been discouraged from receiving live-virus vaccines. Some speculate that children with metabolic disorders might be prone to vaccine side effects. Safer vaccines and manufacturing processes are also in the works. New influenza vaccine doses are produced in cell culture, rather than the industry-standard chicken eggs. This process will improve reliability and reduce allergic reactions to egg proteins. Researchers are also developing replacements for vaccines that can be risky for vulnerable groups. These include current smallpox vaccines that cannot safely be given to immunocompromised people; the tuberculosis vaccine, which is not recommended for HIV-positive infants; and the yellow-fever vaccine, which puts elderly people at particular risk of a yellow-fever-like illness. Researchers are quick to emphasize that the benefits of vaccines still greatly outweigh the risks.



Figure: **Preparation of Measles Vaccine**: Workers preparing measles vaccine in chicken eggs.

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SECTION OVERVIEW

12.2: Immunoassays for Disease

Topic hierarchy

12.2A: Immunoassays for Disease

12.2B: Antibody Functions

12.2C: Serology

12.2D: Precipitation Reactions

12.2E: Agglutination Reactions

12.2F: Neutralization Reaction

12.2G: Complement Fixation

12.2H: Fluorescent Antibodies

12.2I: Enzyme-Linked Immunosorbent Assay (ELISA)

12.2J: Immunoblot Procedures

12.2K: Tests That Differentiate Between T Cells and B cells

12.2L: In Vivo Testing

12.2M: The Future of Diagnostic Immunology

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12.2A: Immunoassays for Disease

Immunoassays are laboratory techniques based on the detection of antibody production in response to foreign antigens.

Learning Objectives

- Describe how immunoassays aid in the diagnosis of disease

Key Points

- When microbial agents penetrate the body, they elicit an immune response that involves cellular and humoral components.
- An immune response is usually characterized by antibody secretions. These can be measured in the laboratory through various biochemical and serological techniques.
- Most immunoassays rely on the formation of antibody- antigen complexes that can be identified using an indicator molecule.

Key Terms

- **humoral**: Of or relating to the body fluids or humours.
- **antibody**: A protein produced by B-lymphocytes that binds to a specific antigen.

The Immune System

Immunology is the study of molecules, cells, and organs that make up the immune system. The function of the immune system is to recognize self antigens from non-self antigens and defend the body against non-self (foreign) agents. Through specific and non-specific defense mechanisms, the body's immune system is able to react to microbial pathogens and protect against disease. The first line of defense against infection is intact skin, mucosal membrane surfaces, and secretions that prevent pathogens from penetrating into the body.

When a foreign agent penetrates the first line of resistance, an immune reaction is elicited and immune cells are recruited into the site of infection to clear microorganisms and damaged cells by phagocytosis. If the inflammation remains aggravated, antibody-mediated immune reaction is activated and different types of immune cells are engaged to resolve the disease. The immune system is composed of cellular and humoral elements. The cellular component includes mast cells, neutrophils, macrophages, T and B lymphocytes, and plasma cells. The humoral component includes complement, lyzozyme, interferon, antibodies, and cytokines. All work cooperatively to eliminate immunogenic foreign substances from the body.

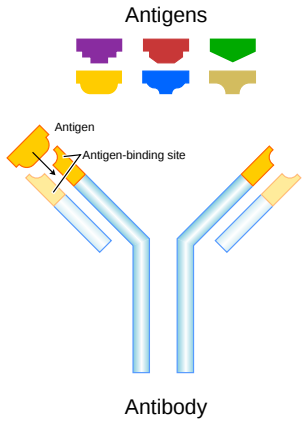

Figure: **Immune complex**: This is the complex formation of a specific antibody-antigen.

Immunoassays

To aid in the diagnosis of disease caused by infectious microorganisms, immunoassays have been developed. These biochemical and serological techniques are based on the detection and quantitation of antibodies generated against an infectious agent, a microbe, or non-microbial antigen.

Because antibodies can be produced against any type of macromolecule, antibody-based techniques are useful in identifying molecules in solution or in cells. A blood sample is collected from the patient during the acute phase of the disease when antibody levels are high. Serum is then isolated and the concentration of antibodies is measured through various methods. Most assays rely

on the formation of large immune complexes when an antibody binds to a specific antigen which can be detected in solution or in gels. Recent methods employ pure antibodies or antigens that have been immobilized on a platform and that can be measured using an indicator molecule. These methods provide high sensitivity and specificity and have become standard techniques in diagnostic immunology.

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12.2B: Antibody Functions

Antibodies, part of the humoral immune response, are involved in pathogen detection and neutralization.

Learning Objectives

- Differentiate among affinity, avidity, and cross-reactivity in antibodies

Key Points

- Antibodies are produced by plasma cells, but, once secreted, can act independently against extracellular pathogen and toxins.
- Antibodies bind to specific antigens on pathogens; this binding can inhibit pathogen infectivity by blocking key extracellular sites, such as receptors involved in host cell entry.
- Antibodies can also induce the innate immune response to destroy a pathogen, by activating phagocytes such as macrophages or neutrophils, which are attracted to antibody-bound cells.
- Affinity describes how strongly a single antibody binds a given antigen, while avidity describes the binding of a multimeric antibody to multiple antigens.
- A multimeric antibody may have individual arms with low affinity, but have high overall avidity due to synergistic effects between binding sites.
- Cross reactivity occurs when an antibody binds to a different-but-similar antigen than the one for which it was raised; this can increase pathogen resistance or result in an autoimmune reaction.

Key Terms

- **avidity**: the measure of the synergism of the strength individual interactions between proteins
- **affinity**: the attraction between an antibody and an antigen

Antibody Functions

Differentiated plasma cells are crucial players in the humoral immunity response. The antibodies they secrete are particularly significant against extracellular pathogens and toxins. Once secreted, antibodies circulate freely and act independently of plasma cells. Sometimes, antibodies can be transferred from one individual to another. For instance, a person who has recently produced a successful immune response against a particular disease agent can donate blood to a non-immune recipient, confering temporary immunity through antibodies in the donor's blood serum. This phenomenon, called passive immunity, also occurs naturally during breastfeeding, which makes breastfed infants highly resistant to infections during the first few months of life.

Antibodies coat extracellular pathogens and neutralize them by blocking key sites on the pathogen that enhance their infectivity, such as receptors that "dock" pathogens on host cells. Antibody neutralization can prevent pathogens from entering and infecting host cells, as opposed to the cytotoxic T-cell-mediated approach of killing cells that are already infected to prevent progression of an established infection. The neutralized antibody-coated pathogens can then be filtered by the spleen and eliminated in urine or feces.

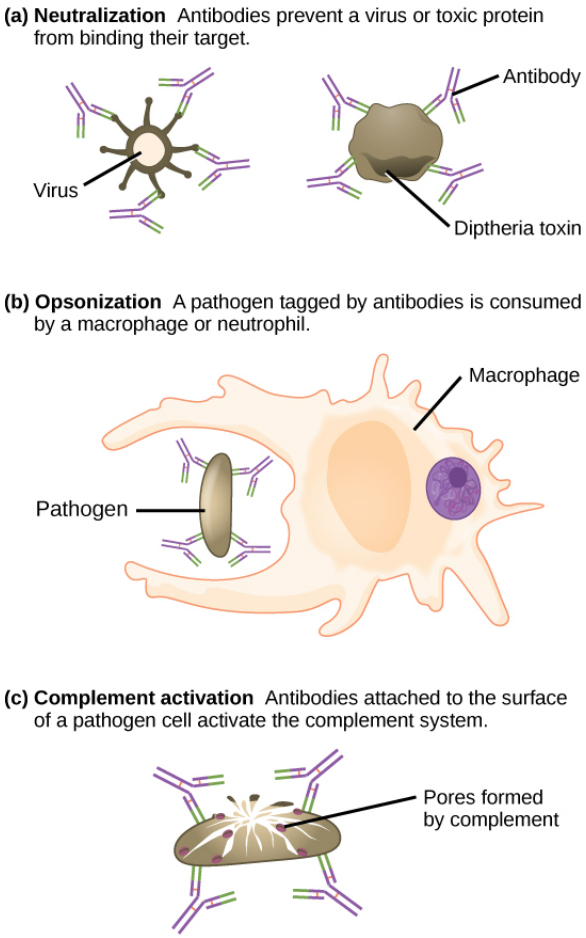

Figure: **Mechanisms of antibody action**: Antibodies may inhibit infection by (a) preventing the antigen from binding to its target, (b) tagging a pathogen for destruction by macrophages or neutrophils, or (c) activating the complement cascade.

Antibodies also mark pathogens for destruction by phagocytic cells, such as macrophages or neutrophils, because they are highly attracted to macromolecules complexed with antibodies. Phagocytic enhancement by antibodies is called opsonization. In another process, complement fixation, IgM and IgG in serum bind to antigens, providing docking sites onto which sequential complement proteins can bind. The combination of antibodies and complement enhances opsonization even further, promoting rapid clearing of pathogens.

Affinity, avidity, and cross reactivity

Not all antibodies bind with the same strength, specificity, and stability. In fact, antibodies exhibit different affinities (attraction) depending on the molecular complementarity between antigen and antibody molecules. An antibody with a higher affinity for a particular antigen would bind more strongly and stably. It would be expected to present a more challenging defense against the pathogen corresponding to the specific antigen.

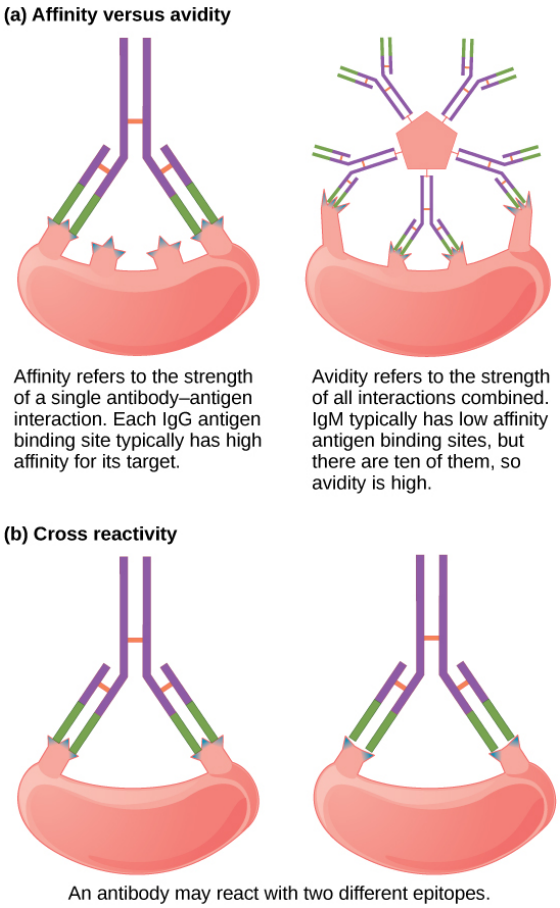

Figure: **Antibody affinity, avidity, and cross reactivity**: (a) Affinity refers to the strength of single interactions between antigen and antibody, while avidity refers to the strength of all interactions combined. (b) An antibody may cross-react with different epitopes.

The term avidity describes binding by antibody classes that are secreted as joined, multivalent structures (such as IgM and IgA). Although avidity measures the strength of binding, just as affinity does, the avidity is not simply the sum of the affinities of the antibodies in a multimeric structure. The avidity depends on the number of identical binding sites on the antigen being detected, as well as other physical and chemical factors. Typically, multimeric antibodies, such as pentameric IgM, are classified as having lower affinity than monomeric antibodies, but high avidity. Essentially, the fact that multimeric antibodies can bind many antigens simultaneously balances their slightly-lower-binding strength for each antibody/antigen interaction.

Antibodies secreted after binding to one epitope on an antigen may exhibit cross reactivity for the same or similar epitopes on different antigens. Cross reactivity occurs when an antibody binds not to the antigen that elicited its synthesis and secretion, but to a different antigen. Because an epitope corresponds to such a small region (the surface area of about four to six amino acids), it is possible for different macromolecules to exhibit the same molecular identities and orientations over short regions.

Cross reactivity can be beneficial if an individual develops immunity to several related pathogens despite having been exposed to or vaccinated against only one of them. For instance, antibody cross reactivity may occur against the similar surface structures of various Gram-negative bacteria. Conversely, antibodies raised against pathogenic molecular components that resemble self molecules may incorrectly mark host cells for destruction, causing autoimmune damage. Patients who develop systemic lupus erythematosus (SLE) commonly exhibit antibodies that react with their own DNA. These antibodies may have been initially raised against the nucleic acid of microorganisms, but later cross-reacted with self-antigens. This phenomenon is also called molecular mimicry.

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12.2C: Serology

Serology is the study of blood serum and other bodily fluids for the identification of antibodies.

Learning Objectives

- Describe how serology can be used to identify antibodies in blood serum and other bodily fluids

Key Points

- Serology is based on detecting immunoglobulin levels during the course of an infection.
- Serological techniques can differentiate between IgM and IgG antibodies, thus determining the stage of the infection.
- Serological techniques are important for the diagnosis of immunological diseases.

Key Terms

- **immunoglobulin G**: Most abundant antibody isotype secreted by plasma B cells.
- **immunoglobulin M**: largest antibody produced by B cells and the first to appear in response to initial exposure to antigen.
- **serology**: the scientific study of blood serum and other bodily fluids.

Serology is the scientific study of blood serum and other bodily fluids. In practical immunological terms, serology is the diagnostic identification of antibodies in the serum. Serological tests are performed on blood serum, and body fluids such as semen and saliva. In practice, the term usually refers to the diagnostic identification of antibodies in the serum or the detection of antigens of infectious agents in serum. Such antibodies are typically formed in response to an infection (against a given microorganism), against other foreign proteins (in response, for example, to a mismatched blood transfusion), or to one's own proteins (in instances of autoimmune disease).

A primary immune response occurs when a B cell sees an antigen for the first time. Antigen binding to the surface of the B cell stimulates the production of antibodies that are capable of binding directly to the antigen. Because this first recognition process takes time for antibody development, there is an initial delay for the body to fight the invading antigens. Immunoglobulin M (IgM) is an antibody produced during the primary immune response and plays a significant role fighting infection. When an antigen is introduced into the body for the first time, large quantities of IgM are produced. Meanwhile, the B cells are producing highly specific Immunoglobulin G (IgG) more slowly. Once IgG is produced in quantity, the IgG plays a greater role in the removal of antigens from the body due to its ability to bind to the antigen molecules more tightly. Through the course of an infection, a rapid spike of circulating IgM can be seen in the bloodstream. This is followed by a decrease of IgM as the amount of IgG increases. Medical laboratory personnel can identify the course and duration of an infection by measuring the ratio of IgM to IgG in the bloodstream. A ratio high in IgM indicates that an infection is in its early stages, while a ratio high in IgG indicates that the infection is in its later stage.

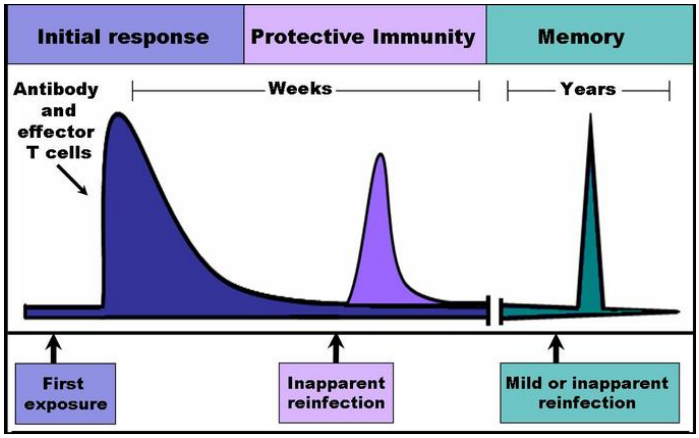

Figure: **Immune response**: When B and T cells begin to replicate, some of the offspring that they produce will end up becoming long-lived memory cells. These memory cells will remember all specific pathogens encountered during the animal's lifetime and can thus call forth a strong response if the pathogen ever invades the body again.

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12.2D: Precipitation Reactions

Precipitation reactions are serological assays for the detection of immunoglobulin levels from the serum of a patient with infection.

Learning Objectives

- Describe how precipitation reactions can be used for the detection of immunoglobulin levels in the serum of a patient

Key Points

- Precipitation assays are performed in semi-solid media such as agar or agarose where antibodies and antigens can diffuse toward one another and form a visible line of precipitation.
- There are several precipitation methods applied in the diagnostic laboratory. These include single, double, and electroimmunodiffusion.
- The most widely used gold standard precipitation methods are Ouchterlony test and Mancini test.

Key Terms

- **precipitin**: Any antibody which reacts with an antigen to form a precipitate.

Precipitation reactions are based on the interaction of antibodies and antigens. They are based on two soluble reactants that come together to make one insoluble product, the precipitate. These reactions depend on the formation of lattices (cross-links) when antigen and antibody exist in optimal proportions. Excess of either component reduces lattice formation and subsequent precipitation. Precipitation reactions differ from agglutination reactions in the size and solubility of the antigen and sensitivity. Antigens are soluble molecules and larger in size in precipitation reactions. There are several precipitation methods applied in clinical laboratory for the diagnosis of disease. These can be performed in semisolid media such as agar or agarose, or non-gel support media such as cellulose acetate.

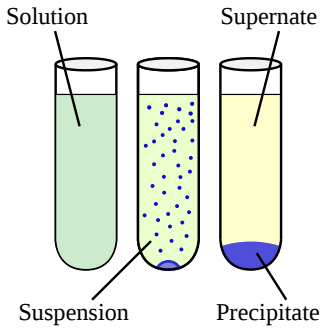

Figure: **Precipitation reaction**: Difference in the visual appearance of an aggregate and a precipitate.

Precipitation methods include double immunodiffusion (qualitative gel technique that determines the relationship between antigen and antibody), radial immunodiffusion (semi-quantitation of proteins by gel diffusion using antibody incorporated in agar), and electroimmunodiffusion (variation of the double immunodiffusion method reaction that uses an electric current to enhance the mobility of the reactants toward each other). Precipitation reactions are less sensitive than agglutination reactions but remain gold standard serological techniques. The most commonly used serologic precipitation reactions are the Ouchterlony test (based on double immunodiffusion and named after the Swedish physician who invented it), and the Mancini method (based on single radial immunodiffusion). In the double immunodiffusion technique, three basic reaction patterns result from the relationship of antigens and antibodies. These patterns are identity, non-identity, and partial identity. The Mancini method results in precipitin ring formation on a thin agarose layer. The diameter of the ring correlates with the concentration of proteins in the precipitin.

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12.2E: Agglutination Reactions

Agglutination reactions are used to assess the presence of antibodies in a specimen by mixing it with particulate antigens.

Learning Objectives

- Describe how agglutination reactions can be used to assess the presence of antibodies in a specimen

Key Points

- Agglutination reactions produce visible aggregates of antibody – antigen complexes when antibodies or antigens are conjugated to a carrier.
- Carriers used in agglutination methods could be artificial (e.g., latex or charcoal) or biological (e.g., erythrocytes).
- There are various methods of agglutination reactions that follow the same principle, but they differ in the elements they employ based on the desired endpoint and the main purpose of the test.

Key Terms

- **avidity**: The measure of the synergism of the strength of individual interactions between proteins.
- **erythrocytes**: Red blood cells.
- **agglutination**: the clumping together of red blood cells or bacteria, usually in response to a particular antibody

Agglutination is the visible expression of the aggregation of antigens and antibodies. Agglutination reactions apply to particulate test antigens that have been conjugated to a carrier. The carrier could be artificial (such as latex or charcoal particles) or biological (such as red blood cells). These conjugated particles are reacted with patient serum presumably containing antibodies. The endpoint of the test is the observation of clumps resulting from that antigen-antibody complex formation. The quality of the result is determined by the time of incubation with the antibody source, amount and avidity of the antigen conjugated to the carrier, and conditions of the test environment (e.g., pH and protein concentration). Various methods of agglutination are used in diagnostic immunology and these incude latex agglutination, flocculation tests, direct bacterial agglutination, and hemagglutination.

In latex agglutination, many antibody molecules are bound to latex beads (particles), which increases the number of antigen-binding sites. If an antigen is present in a test specimen, it will bind to the antibody and form visible, cross-linked aggregates. Latex agglutination can also be performed with the antigen conjugated to the beads for testing the presence of antibodies in a serum specimen.

Flocculation tests are designed for antibody detection and are based on the interaction of soluble antigens with antibodies, producing a precipitate of fine particles that can be seen with the naked eye.

Direct bacterial agglutination uses whole pathogens as a source of antigen. It measures the antibody level produced by a host infected with that pathogen. The binding of antibodies to surface antigens on the bacteria results in visible clumps.

Hemagglutination uses erythrocytes as the biological carriers of bacterial antigens, and purified polysaccharides or proteins for determining the presence of corresponding antibodies in a specimen.

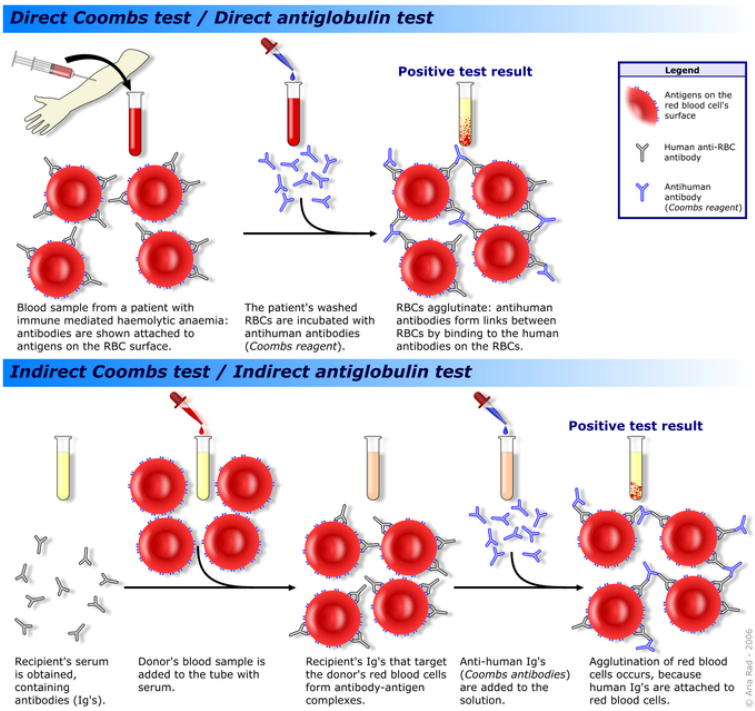

Figure: **Hemagglutination assay**: Red blood cells are used as carriers to detect antibodies from a patient's serum.

Agglutination tests are easy to perform and in some cases are the most sensitive tests currently available. These tests have a wide range of applications in the clinical diagnosis of non- infectious immune disorders and infectious disease.

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12.2F: Neutralization Reaction

Neutralization reactions are used to inactivate viruses and evaluate neutralizing antibodies.

Learning Objectives

- Describe how neutralizing antibodies serve to block viral attachment to cells thus inhibiting viral replication

Key Points

- When a vertebrate is infected with a virus, antibodies are produced against it. Some of the antibodies can block viral infection by neutralization which is usually the result of a formation of a virus-antibody complex. This complex can prevent viral infections in many ways.
- Neutralizing antibodies have shown potential in the treatment of retroviral infections such as HIV. Recently, potent and broadly neutralizing human antibodies against influenza have been reported.
- In diagnostic immunology and virology laboratories, the evaluation of neutralizing antibodies, which destroy the infectivity of viruses, can be measured by the neutralization method.

Key Terms

- **neutralization**: In the immunological sense refers to the ability of antibodies to block the site(s) on bacteria or viruses that they use to enter their target cell. One example of this within biology is a neutralizing antibody.
- **virion**: A single individual particle of a virus (the viral equivalent of a cell).
- **endosomes**: membrane-bound compartments inside eukaryotic cells.

A neutralizing antibody defends a cell from an antigen or infectious body by inhibiting or neutralizing any effect it has biologically. The antibody response is crucial for preventing many viral infections and may also contribute to the resolution of an infection. When a vertebrate is infected with a virus, antibodies are produced against many epitopes of multiple virus proteins. A subset of these antibodies can block viral infection by a process called neutralization. This usually involves the formation of a virus-antibody complex.

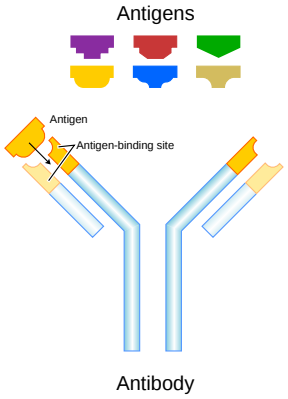

Figure: **Neutralizing antibody**: Antibody neutralizing an antigen and preventing its biological effect.

This virus-antibody complex can prevent viral infections in many ways. It may interfere with virion binding to receptors, block uptake into cells, prevent uncoating of the genomes in endosomes, or cause aggregation of virus particles. Many enveloped viruses are lysed when antiviral antibodies and serum complement disrupt membranes. Antibodies can also neutralize viral infectivity by binding to cell surface receptors.

Neutralizing antibodies have shown potential in the treatment of retroviral infections. Medical professionals and researchers have shown how the encoding of genes which influence the production of this particular type of antibody could help in the treatment of infections that attack the immune system. Experts in the field have used HIV treatment as an example of infections these antibodies can treat. Recently, potent and broadly neutralizing human antibodies against influenza have been reported, and have suggested possible strategies to generate an improved vaccine that would confer long-lasting immunity. Another disease which has been linked to the production of neutralizing antibodies is multiple sclerosis.

In diagnostic immunology and virology laboratories, the evaluation of neutralizing antibodies, which destroy the infectivity of viruses, can be measured by the neutralization method. In this procedure, patient serum is mixed with a suspension of infectious virus particles of the same type as those suspected of causing disease in the patient. A control suspension of virus is mixed with normal serum and is then inoculated into an appropriate cell culture. If the patient serum contains antibody to the virus, the antibody will bind to the virus particles and prevent them from invading the cells in culture, thereby neutralizing the infectivity of the virus. This technique is labor-intensive, demanding, and time consuming. It application is restricted to laboratories that perform routine viral cultures and related diagnosis.

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12.2G: Complement Fixation

Complement fixation is a method that demonstrates antibody presence in patient serum.

Learning Objectives

- Describe how the complement fixation assay can be used to test for the presence of a specific antibody in a patient's serum

Key Points

- Complement fixation method is more demanding than other systems used to detect antibodies and has been replaced by more sensitive techniques.
- Complement fixation requires several elements mixed together in optimum concentrations.
- The indicator system for the complement fixation assay is sheep red blood cells bound to anti-sheep immunoglobulin G.

Key Terms

- **immunoglobulin G**: Most abundant antibody isotype secreted by plasma B cells.

Complement fixation is a classic method for demonstrating the presence of antibody in patient serum. The complement fixation test consists of two components. The first component is an indicator system that uses combination of sheep red blood cells, complement-fixing antibody such as immunoglobulin G produced against the sheep red blood cells and an exogenous source of complement usually guinea pig serum. When these elements are mixed in optimum conditions, the anti-sheep antibody binds on the surface of red blood cells. Complement subsequently binds to this antigen -antibody complex formed and will cause the red blood cells to lyse.

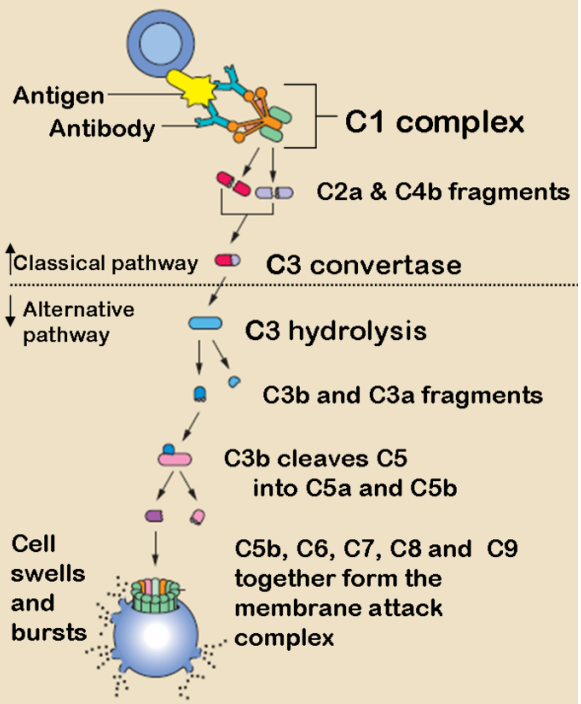

Figure: **The complement pathway**: Complement binds to antigen-antibody complex and leads to cell lysis.

The second component is a known antigen and patient serum added to a suspension of sheep red blood cells in addition to complement. These two components of the complement fixation method are tested in sequence. Patient serum is first added to the known antigen, and complement is added to the solution. If the serum contains antibody to the antigen, the resulting antigen-antibody complexes will bind all of the complement. Sheep red blood cells and the anti-sheep antibody are then added. If complement has not been bound by an antigen-antibody complex formed from the patient serum and known antigens, it is available to bind to the indicator system of sheep cells and anti-sheep antibody. Lysis of the indicator sheep red blood cells signifies both a lack of antibody in patient serum and a negative complement fixation test. If the patient's serum does contain a complement-fixing antibody, a positive result will be indicated by the lack of red blood cell lysis.

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12.2H: Fluorescent Antibodies

Fluorescent antibodies are antibodies that have been tagged with a fluorescent compound to facilitate their detection in the laboratory.

Learning Objectives

- Describe how fluorescent antibody conjugates can be used in immunoassays for protein detection

Key Points

- Fluorescent labeling of antibodies is used in place of radioisotopes and enzymes to enhance the sensitivity and specificity of immunological tests.
- Fluorescent antibodies can be used to stain proteins from patient serum or tissue sections fixed on a slide or live cells in suspension.
- Fluorescent antibodies can be detected with a fluorescent microscope or a flow cell sorter.

Key Terms

- **radioisotope**: A radioactive isotope of an element.

Fluorescent labeling is another method of demonstrating the complexity of antigens and antibodies. Fluorescent molecules are used as substitutes for radioisotope or enzyme labels. The fluorescent antibody technique consists of labeling antibody with dyes such as fluorescein isothiocyanate (FITC). These compounds have high affinity for proteins with which they conjugate.

Fluorescent techniques are very specific and sensitive, so fluorescent antibody-based techniques require a fluorescent microscope. A fluorescent substance absorbs light of one wavelength and emits light of a longer wavelength. Fluorescein fluoresces an intense apple-green color when excited under fluorescent microscopy. The chemical manipulation in labeling antibodies with fluorescent dyes to permit detection by direct microscopy examination does not impair antibody activity.



Figure: **Flow cell sorter**: This instrument is used to analyze live cells in suspension after staining them with fluorescent antibodies.

After the labeling of a specific antibody with a fluorescent molecule, it can still be reacted with its antigen and identified microscopically. Fluorescent antibody conjugates are commonly used in immunoassays. The basic methods utilizing fluorescent antibodies include direct, inhibition, and indirect immunofluorescent assay.

In the direct technique, a fluorescent antibody is used to detect antigen-antibody reactions at a microscopic level. The inhibition immunofluorescent assay is a blocking test in which an antigen is first exposed to an unlabeled antibody, then to a fluorescent antibody, and is finally washed and examined. Indirect immunofluorescence assay is based on the ability of antibodies to react with antigens as well as act as antigens and react with anti-antibody (anti-immunoglobulin). This technique is used extensively for the detection of autoantibodies and antibodies to tissue and cellular antigens. The methods described are mostly performed on glass slides with patient serum or tissue sections. Immunofluorescence can also be performed to identify specific antigens on live cells in suspension. This method is known as flow cytometry and requires a flow cell sorter rather than a fluorescent microscope.

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12.2I: Enzyme-Linked Immunosorbent Assay (ELISA)

Enzyme-linked immunosorbent assay (ELISA) is a solid-phase enzyme immunoassay used to detect the presence of a substance in solution.

Learning Objectives

- Describe how the Enzyme-linked immunosorbent assay (ELISA) can be used to detect and quantitate antigens, antibodies and allergens

Key Points

- ELISA is a quantitative technique that measures serum concentration of antigens, antibodies, and allergens.
- Standard ELISA uses antibody-antigen-antibody trapping principle with the second antibody coupled to an enzyme. If the complex is formed, the enzyme converts a clear solution into a colored one that can be measured with a spectrophotometer.
- ELISA is performed in a muti-well microtiter plate. In addition to the test solution, standard solutions are added with known antigen concentration. These solutions will be used to infer the concentration of the antigen being tested.

Key Terms

- **spectrophotometrically**: By using spectrophotometry.
- **epitope**: That part of a biomolecule (such as a protein) that is the target of an immune response.

Enzyme-linked immunosorbent assay (ELISA) is a method of quantifying an antigen immobilized on a solid surface. ELISA uses a specific antibody with a covalently coupled enzyme. The amount of antibody that binds the antigen is proportional to the amount of antigen present, which is determined by spectrophotometrically measuring the conversion of a clear substance to a colored product by the coupled enzyme.

Several variations of ELISA, seen in, exist but the most commonly used method is the sandwich ELISA. The sandwich assay uses two different antibodies that are reactive with different epitopes on the antigen with a concentration that needs to be determined. A fixed quantity of one antibody is attached to a series of replicate solid supports, such as plastic microtiter multi-well plate. Test solutions containing antigen at an unknown concentration are added to the wells and allowed to bind. Unbound antigen is removed by washing, and a second antibody which is linked to an enzyme is allowed to bind. This second antibody-enzyme complex constitutes the indicator system of the test. The antigen serves as bridge, so the more antigen in the test solution, the more enzyme-linked antibody will bind. The test solution is used in parallel with a series of standard solutions with known concentrations of antigen that serve as control and reference. The results obtained from the standard solutions are used to construct a binding curve of the second antibody as a function of antigen concentration. The concentration of antigens can be inferred from absorbance readings of standard solutions.

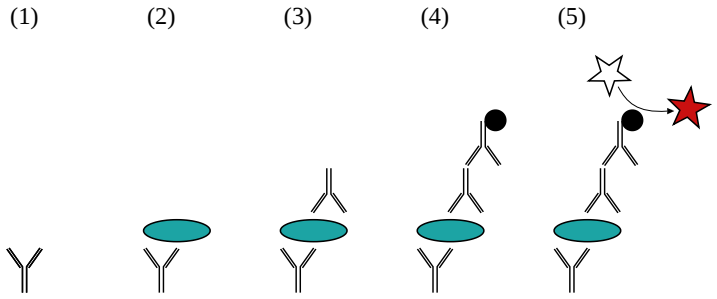

Figure: **Sandwich ELISA**: Two antibodies recognize different epitopes on same antigen.

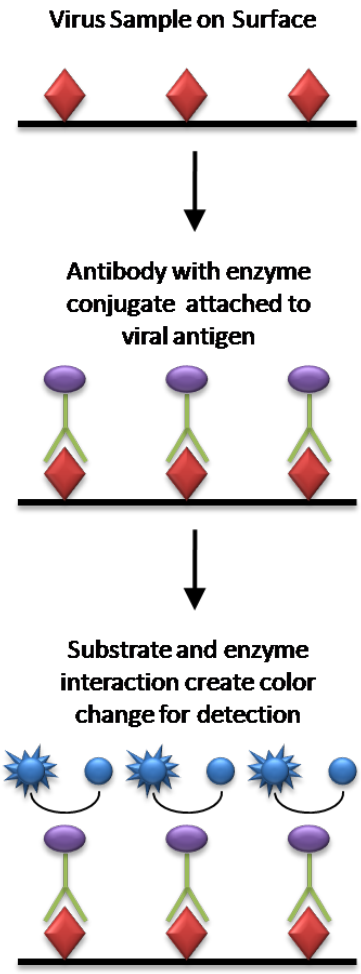

Figure: **ELISA**: Direct ELISA diagram using a viral antigen as an example.

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12.2J: Immunoblot Procedures

Immunoblot is a technique for analyzing proteins via antigen-antibody specific reactions.

Learning Objectives

- Describe how Western blotting allows individuals to detect specific solubilized proteins from serum or cell or tissue extracts

Key Points

- In immunoblot techniques such as Western blot analysis, proteins are separated by electrophoresis and transferred onto nitrocellulose sheets, then are identified by their reaction with labeled antibodies.
- Electrophoresis uses an electric current to separate proteins based on their size. Big proteins migrate slower and are represented by the highest bands on the blot, while small proteins migrate faster and are indicated by the lowest bands on the blot.
- Immunoblot assays are usually performed to confirm results obtained by other techniques such as ELISA.

Key Terms

- **sodium dodecyl sulfate**: strong detergent agent used to reduce and unfold native protein.
- **blot**: method of transferring protein, DNA, or RNA onto a carrier membrane.

Immunoblot procedures like protein blotting, or Western blotting, allow individuals to detect specific solubilized proteins from extracts made from cells or tissues, before or after any purification steps.

Immunoblotting Procedures

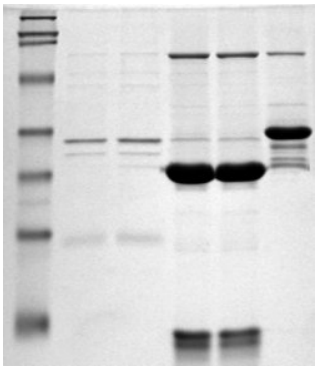

Figure: **Immunoblot**: proteins separated by molecular weight and represented by a dark band on a blot.

This analytic technique proceeds in the following steps. Proteins are generally separated by size using sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis. After this, they are transferred to a synthetic membrane via dry, semi-dry, or wet blotting methods. In the electric field generated by a power supply, the proteins coated with negatively charged SDS migrate toward the positive electrode. As the proteins migrate out of the gel, they are captured on a membrane. Protein binding to the membrane is an irreversible mechanism. Membranes can be of the nitrocellulose, polyvinylidene difluoride (PVDF), or nylon variety. The membrane can then be blocked with serum albumin or milk solution to prevent non-specific antibody binding. This is followed by probing with antibodies specific to the protein being studied on the membrane, a method that is similar to immunohistochemistry, but without a need for fixation. This technique exploits the specificity inherent in antigen-antibody recognition. Detection is typically performed using chromogen or peroxide-linked secondary antibodies to catalyze a chromogenic or chemiluminescent reaction.

Applications of Immunoblotting

Western blotting is a routine molecular biology method that can be used to semi-quantitatively compare protein levels between extracts. The size separation, prior to blotting, allows the protein molecular weight to be gauged, as compared with known molecular weight markers. Immunoblots are most often used in research settings and are usually performed to confirm results from ELISA or other immunoassays. In clinical diagnostic settings, immunoelectrophoresis is applied, which involves the

electrophoresis of serum or urine followed by immunodiffusion. The size and position of precipitation bands provides the same type of information about antibody amount as the double immunodiffusion method.

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12.2K: Tests That Differentiate Between T Cells and B cells

Methods used to differentiate T cells and B cells include staining cell surface receptors and functional assays like the T lymphocyte cytotoxicity assay.

Learning Objectives

- Describe how T cells and B cells can be differentiated using staining of cell surface receptors and functional assays like the T lymphocyte cytotoxicity assay

Key Points

- There are two types of lymphocytes: B cells and T cells. These two components of the immune system have different functions but cooperate to fight infection.
- T cells elicit cell-mediated immune response, while B cells elicit humoral immunity.
- Lymphocytes are the only immunologically specific cellular components of the immune system.

Key Terms

- **cytotoxic**: of, relating to, or being a cytotoxin

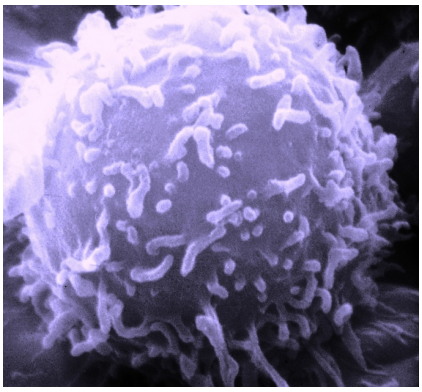

Figure: **SEM Lymphocyte**: A scanning electron microscope (SEM) image of a single human lymphocyte.

Lymphocytes are the only immunologically specific cellular components of the immune system. They are divided into two types based on the pathogen recognition receptors they express on their surface. T cells or T lymphocytes belong to a group of white blood cells known as lymphocytes. They are called T cells because they mature in the thymus. They play a central role in cell-mediated immunity along with initiating rejection of foreign tissues following organ transplantation. B-cells are also white blood cells and are a vital part of the humoral immunity branch of the adaptive immune system. These two cell types can function independently or cooperatively to defend the body against pathogens. T-lymphocytes can be distinguished from other lymphocytes like B cells and natural killer cells (NK cells) by the presence of a T cell receptor (TCR) on the cell surface. Alternatively, B-cells can be distinguished from other lymphocytes like T cells and natural killer cells (NK cells) by the presence of a protein on the B-cell's outer surface called a B-cell receptor (BCR).

Traditionally, T-lymphocytes were defined by their ability to form E-rosettes when they bind selectively to sheep erythrocytes. T-lymphocytes express CD3, CD4, CD8, or CD25 markers. B-lymphocytes express CD19 marker. The expression of different markers allows the separation/ differentiation of T and B cells. Another functional assay used to identify T-lymphocyte is the cytotoxic activity assay. This assay is based on measuring the killing ability that a determined number of T lymphocytes have for a certain number of target cells when both populations are placed together. B-lymphocytes have membrane-bound immunoglobulins that can be stained with anti-immunoglobulin labeled with fluorescent dyes and detected with a fluorescent microscope. More modern techniques like flow cytometry and immunohistochemistry are commonly used and rely on the use of fluorescent antibodies. These techniques are based on staining B and T cells for unique cell surface markers known as cluster of differentiation (CD).

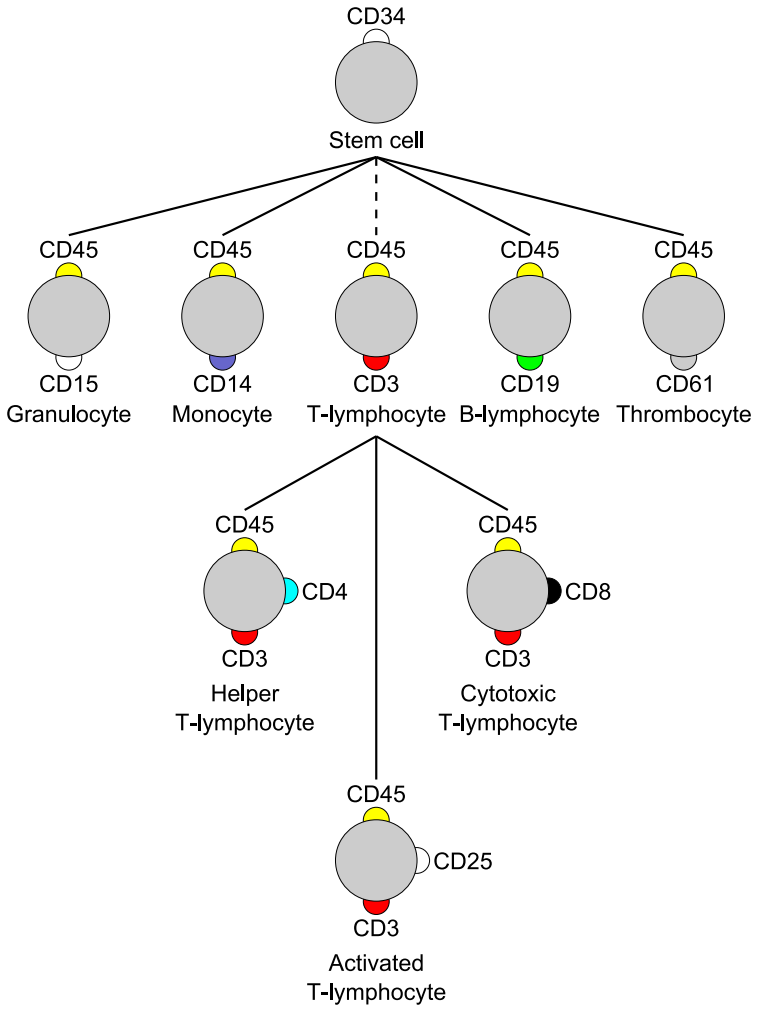

Figure: **Cluster of differentiation**: T and B lymphocytes express unique CD markers.

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12.2L: In Vivo Testing

In vivo testing using animal models of disease help discover new ways of solving complex health problems.

Learning Objectives

- Describe how animals can be used for diagnostic antibody production

Key Points

- In vivo testing is necessary for medical and research purposes. The medical field benefits from animal models to test the safety of drugs before they are used on patients. The research field benefits from in vivo testing by validating in vitro findings in vertebrates closest to humans.
- The most used animal models are mice, rats, and other rodents.
- In vivo testing is useful for the production of polyclonal antibodies applied in immunoassays and diagnostic immunology.

Key Terms

- **in vitro**: In an artificial environment outside the living organism.
- **antiserum**: a serum prepared from human or animal sources containing antigens specific for combatting an infectious disease
- **in vivo**: Within a living organism.

In Vivo Testing

In vivo methods refer to the use of animals as a conduit to generate purified polyclonal antibody solutions (antiserum) for research purposes. Polyclonal antibodies are applied in immunological assays to diagnose disease.

In vivo testing follows strict guidelines and humane animal use ethics. The protocol for diagnostic antibody production in animals follows multiple steps. Animals are injected with microbes or antigenic fragments that elicit an immune response; the immune response is allowed to develop for 1-2 weeks, after which blood is harvested. This blood now contains antibodies created from the antigens that were introduced into the animals. Antibodies are purified from the serum to make antiserum or a purified antibody solution for one particular antigen.



Figure: **A white laboratory rat**: Animals are used in laboratory experiments to translate in vitro findings.

These preparations will produce multiple antibody types that recognize different epitopes on the antigen, hence the term polyclonal. Polyclonal antibodies have various applications in the clinic and in research laboratories. Animals are also used to model human diseases in the research field. They are useful vehicles to understand how our bodies work, find cures and treatments for diseases, test new drugs for safety, and evaluate medical procedures before they are used on patients.

Mice, and other rodents such as rats and hamsters, make up over 90% of the animals used in biomedical research. In addition to having bodies that work similar to humans and other animals, rodents are small in size, easy to handle, relatively inexpensive to buy and keep, and produce many offspring in a short period of time. In vivo testing remains a crucial step for the evaluation of in vitro experimental findings and the production of immunological solutions needed for the diagnosis of human diseases.

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12.2M: The Future of Diagnostic Immunology

The future of diagnostic immunology lies in the production of specific antibody-based assays and the development of improved vaccines.

Learning Objectives

- Describe how immunologic methods are used in the treatment and prevention of infectious diseases and immune-mediated diseases

Key Points

- Diagnostic immunology has considerably advanced due to the development of automated methods.
- New technology takes into account saving samples, reagents, and reducing cost.
- The future of diagnostic immunology faces challenges in the vaccination field for protection against HIV and as anti-cancer therapy.

Key Terms

- **ELISA**: enzyme-linked immunosorbent assay; assay based on the principle of antibody-antigen interaction.

The Future of Diagnostic Immunology

Modern immunology relies heavily on the use of antibodies as highly specific laboratory reagents. The diagnosis of infectious diseases, the successful outcome of transfusions and transplantations, and the availability of biochemical and hematologic assays with extraordinary specificity and sensitivity capabilities all attest to the value of antibody detection.

Immunologic methods are used in the treatment and prevention of infectious diseases and in the large number of immune -mediated diseases. Advances in diagnostic immunology are largely driven by instrumentation, automation, and the implementation of less complex and more standardized procedures. Examples of such processes are as follows:

- miniaturization (use of microtiter plates to save samples and reagents),
- amplified immunoassays (chemiluminesent ELISA),
- flow cytometry with monoclonal antibodies,
- immunoglobulins,
- molecular methods (polymerase chain reactions).

These methods have facilitated the performance of tests and have greatly expanded the information that can be developed by a clinical laboratory. The tests are now used for clinical diagnosis and the monitoring of therapies and patient responses. Immunology is a relatively young science and there is still so much to discover. Immunologists work in many different disease areas today that include allergy, autoimmunity, immunodeficiency, transplantation, and cancer.

Interestingly, no matter what the areas of expertise, vaccine development and understanding how vaccines work pose the greatest challenges. The vaccines currently used primarily generate an antibody response, which is able to attack free-moving pathogens, but is unable to fight bacteria and viruses, such as human immunodeficiency virus (HIV). In the cancer research field, vaccines that stimulate the immune system to attack tumor cells are undergoing clinical trials.



Figure: **Antibody sculpture**: Angel of the West is a sculpture by Julian Voss-Andreae based on the antibody structure.

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SECTION OVERVIEW

12.3: Preparations for Diagnosing Infection

Topic hierarchy

12.3A: Specimen Collection

12.3B: Immediate Direct Examination of Specimen

12.3C: Cultivation of Specimen

12.3D: DNA Analysis Using Genetic Probes and PCR

12.3E: Nucleic Acid Sequencing and rRNA Analysis

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12.3A: Specimen Collection

Laboratory diagnosis of diseases begins with the collection of a clinical specimen for examination or processing in the laboratory.

Learning Objectives

- Describe how laboratory diagnosis of disease begins with the collection of a clinical specimen for examination and processing

Key Points

- Specimen collection requires withdrawing blood, cerebrospinal fluid, collecting urine, or swabs from mucosal surfaces.
- Specimen collection is performed using aseptic techniques to ensure sterility of the sample and avoid contamination from bacteria or other bodily fluids.
- The types of biological samples accepted in most clinical laboratories are: serum samples, virology swab samples, biopsy and necropsy tissue, cerebrospinal fluid, whole blood for PCR, and urine samples. These are collected in specific containers for successful processing in the laboratory.

Key Terms

- **PCR**: polymerase chain reaction
- **necropsy**: The pathological dissection of a corpse; particularly to determine cause of death. Applicable to the examination of any life form.
- **biopsy**: The removal and examination of a sample of tissue from a living body for diagnostic purposes.

Laboratory diagnosis of an infectious disease begins with the collection of a clinical specimen for examination or processing in the laboratory.

The laboratory, with the help of well-chosen techniques and methods for rapid isolation and identification, confirms the diagnosis.

It has been observed that the most important and frequent factor affecting laboratory analysis, even in a well-functioning laboratory, is not the laboratory investigation itself but specimen preparation and errors in identification or labeling. Proper collection of an appropriate clinical specimen is, hence, the first step in obtaining an accurate laboratory diagnosis of an infectious disease.

Applying one's knowledge of microbiology and immunology for the collection, transportation and storage of specimens is as important as it is in the laboratory. For starters, the interpretation of the observation may be misleading if the specimen is inadequate.

There are several types of specimens recommended for diagnosis of immunological diseases including: serum samples, virology swab samples, biopsy and necropsy tissue, cerebrospinal fluid, whole blood for PCR, and urine samples.

Serum is the preferred specimen source for serologic testing. Blood specimens are obtained aseptically using approved venipuncture techniques by qualified personnel. Specimens are allowed to clot at room temperature and then are centrifuged. Serum is transferred to tightly-closing plastic tubes and stored at 2 – 8°C before shipment–which should always be prompt. Acute serum should be collected at the onset of symptoms. Convalescent specimens should follow two to four weeks later. Paired sera are tested together.

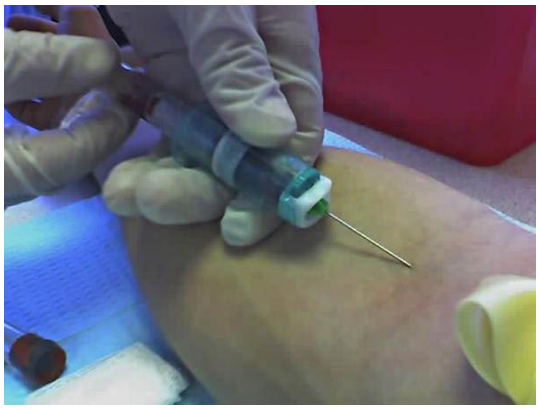

Figure: **Venipuncture**: Performed to draw blood sample using a vacutainer

Plasma is also collected for a very limited number of tests. Lipemic, hemolyzed, or contaminated sera may cause erroneous results and should be avoided as should repeated freeze-thaw cycles.

Another type of specimen used for disease diagnosis is cerebrospinal fluid (CSF). This should be transported in tightly-closing plastic tubes. Refrigerated CSF is acceptable for a limited number of serologic tests; however, if PCR is to be performed for the viral panels, the specimen must be frozen and shipped on dry ice. CSF specimens should be clear of any visible contamination or blood. A lumbar puncture (or LP, and colloquially known as a spinal tap) is performed to collecte CSF. This consists of the insertion of a hollow needle beneath the arachnoid membrane of the spinal cord in the lumbar region to withdraw cerebrospinal fluid for diagnostic purposes or to administer medication.

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12.3B: Immediate Direct Examination of Specimen

Following collection in appropriate containers, clinical specimens undergo a rapid examination in the laboratory.

Learning Objectives

- Describe how immediate direct examination of a specimen is useful to determine microscopic and macroscopic morphology

Key Points

- Immediate direct examination methods depend on the nature of the specimen.
- Diagnostic laboratory techniques include direct testing using a microscope, and immunological or genetic methods that provide immediate clues as to the identity of the microbe or microbes in the sample.
- Phenotypic methods include the examination of microscopic, macroscopic, and biochemical characteristics of a pathogen.

Key Terms

- **biopsied**: to remove and examine a sample of tissue from a living body for diagnostic purposes.

Immediate Direct Examination of Specimen

For specimen collection at sites that normally contain resident microflora, care should be taken to sample only the infected site and not the surrounding areas. For example, throat and nasopharyngeal swabs should not touch the tongue, cheek, or saliva. Saliva is an especially undesirable contaminant because it contains millions of bacteria, of which are normal flora. Sputum, the mucous secretion that coats the lower respiratory surfaces, especially the lungs, is discharged by coughing or taken by a catheterization to avoid contamination with saliva. Also the mucous lining of the vagina, cervix, or urethra can be sampled with a swabbed or applicator stick.

Additional sources of specimens are the vagina, eye, ear canal, nasal cavity (all by swab), and diseased tissue that has been surgically removed (biopsied). Urine is taken aseptically from the bladder with a catheter. Another method called the “clean catch” is taken by washing the external urethra and collecting the urine in midstream. Some diagnostic techniques require first-voided “dirty catch” urine. Sterile materials such as blood, cerebrospinal fluid, and tissue fluid must be taken by sterile needle aspiration.

Diagnostic laboratory techniques include direct testing using a microscope, immunological, or genetic methods that provide immediate clues as to the identity of the microbe or microbes in the sample, and cultivation, isolation, and identification of pathogens using a wide variety of general and specific tests (such as blood or other fluids).

Most tests fall into two categories: presumptive data, which place the isolated microbe in a preliminary category such as genus, and more specific, confirmatory data, which provide more definitive evidence of a species. Some diseases are diagnosed without the need to identify microbes from specimens. Serological tests on a patient’s serum can detect signs of an antibody response. One method that clarifies whether a positive test indicates current or prior infection is to take two samples several days apart and see if the antibody titer is raising. Skin testing can pinpoint a delayed allergic reaction to a microorganism. These tests are important in screening the general population for exposure to an infectious agent such as rubella or tuberculosis.

The main phenotypic methods include the direct examination of specimens, observing the growth of specimen cultures on special media, and biochemical testing of specimen cultures.

MICROSCOPIC MORPHOLOGY

Traits that can be valuable aids to identification of cell shape and size, Gram-stain reaction, acid-fast reaction and special structures, including endospores, granules, and capsules. Electron microscopes can pinpoint additional features such as cell wall flagella, pili, and fimbriae.

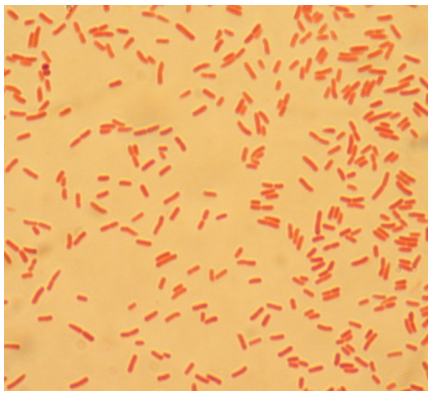

Figure: **Microscopic examination of E. coli**: Gram negative E. coli examined under the microscope from a patient with urinary tract infection.

MACROSCOPIC MORPHOLOGY

Traits that can be assessed with the naked eye are also useful in diagnosis. These include the appearance of colonies, including texture, shape, size, pigment, speed of growth, and patterns of growth in broth and gelatin.

PHYSIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS

Enzymes and other biochemical properties of bacteria are reliable and stable expressions of the chemical identity of each species. Diagnostic tests exist for determining the presence of specific enzymes and assessing nutritional and metabolic activities.

Test examples include: fermentation of sugars, capacity to digest or metabolize complex polymers such as proteins and ploysaccharides; production of gas; presence of enzymes such as catalase, oxidase, and decarboxylase; and sensitivity to antimicrobial drugs.

CHEMICAL ANALYSIS

This involves analyzing the types of specific structural substances that the microorganism contains, such as the chemical composition of peptides in the cell wall and lipids in the membrane.

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12.3C: Cultivation of Specimen

Following direct examination, clinical specimens are cultivated to generate more confirmatory data.

Learning Objectives

- Describe how direct microscope observation of a fresh or stained specimen is one of the most rapid methods of determining its characteristics

Key Points

- The success of pathogen identification and treatment depends on how the specimen is collected, handled, and stored.
- Diagnostic laboratory techniques include direct testing using a microscope, and immunological or genetic methods that provide immediate clues as to the identity of the microbe or microbes in the sample.
- Following direct testing, cultivation, isolation, and identification of pathogens using a wide variety of general and specific tests is required.

Key Terms

- **mannitol**: A polyhydroxy alcohol, an isomer of sorbitol, used as an artificial sweetener.
- **MacConkey agar**: A culture medium designed to grow Gram-negative bacteria and differentiate them from lactose fermentation.

Cultivation of Specimen

The success of pathogen identification and treatment depends on how the specimen is collected, handled, and stored. It is also critical that the pathogen is isolated in a pure culture first. Direct microscope observation of a fresh or stained specimen is one of the most rapid methods of determining characteristics. Stains most often employed for bacteria are the gram stain, though they do not work on some organisms.

The direct florescence antibody (DFA) test can highlight the presence of the microbe in patient specimens by means of labeled antibodies. This test is useful for bacteria such as syphilis spirochete, which are not readily cultivated in a laboratory, or if a rapid diagnosis is essential for the survival of a patient.



Figure: **Blood culture**: This blood is cultured in a bottle to detect bloodstream infections.

In most cases, specimens are also inoculated into differential media that define such characteristics as fermentation patters (mannitol salt and MacConkey agar) and as reactions in blood (blood agar). A patient's blood is usually cultured in a special bottle of broth that can be periodically sampled for growth. Work must be done from isolated colonies or pure cultures, as working with mixed or contaminated cultures gives misleading and inaccurate results. From such isolates, clinical microbiologists obtain information about a pathogen's microscopic morphology and staining reactions, culture appearance, motility, oxygen requirements, and biochemical characteristics.

Serological testing uses in-vitro diagnostic testing of serum, has a high degree of specificity and sensitivity, and is based on the specificity an antibody has for its antigen. These techniques do not necessitate a cultivation step. Serum can be directly used in agglutination, precipitation, complement fixation, fluorescent microscopy, and enzyme-linked assays. Results of specimen analysis are entered in the patient's summary chart.

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12.3D: DNA Analysis Using Genetic Probes and PCR

Genotyping of pathogenic isolates provides valuable support during investigations of suspected outbreaks and when tracing infectious diseases.

Learning Objectives

- Describe how genetic probes can be used to detect unique nucleotide sequences within the DNA or RNA or a microorganism

Key Points

- Hybridization can identify a bacterial species by analyzing segments of its DNA.
- Genetic probes are small fragments of DNA or RNA that are complementary to the specific sequences of DNA from a particular microbe.
- This approach is most useful in the detection of infections due to microorganisms that are difficult to culture.

Key Terms

- **polymerase chain reaction**: A technique in molecular biology for creating multiple copies of DNA from a sample; used in genetic fingerprinting etc.

Genetic probes are based on the detection of unique nucleotide sequences with the DNA or RNA of a microorganism. Once such a unique nucleotide sequence, which may represent a portion of a virulence gene or of chromosomal DNA, is found, it is isolated and inserted into a cloning vector (plasmid), which is then transformed into Escherichia coli to produce multiple copies of the probe. The sequence is then reisolated from plasmids and labeled with an isotope or substrate for diagnostic use. Hybridization of the sequence with a complementary sequence of DNA or RNA, follows cleavage of the double-stranded DNA of the microorganism in the specimen. The use of molecular technology in the diagnoses of infectious diseases has been further enhanced by the introduction of gene amplication techniques, such as the polymerase chain reaction (PCR) in which DNA polymerase is able to copy a strand of DNA by elongating complementary strands of DNA that have been initiated from a pair of closely spaced oligonucleotide primers. This approach has had major applications in the detection of infections due to microorganisms that are difficult to culture (e.g., the human immunodeficiency virus), or that have not as yet been successfully cultured (e.g., the Whipple's disease bacillus).

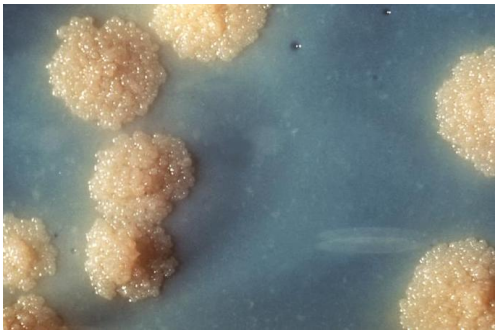

Figure: **Mycobacterium Tuberculosis**: a Mycobacterium tuberculosis culture revealing the organism's colonial morphology.

It is well established that genotyping of pathogenic isolates provides valuable support for the investigation of suspected outbreaks, the detection of unsuspected transmission, the tracing of infectious agents within a community, and the identification of possible sources of infection for newly diagnosed cases. At the national or international level, fingerprinting allows strains from different geographic areas to be compared, and the movement of individual strains to be tracked. Fingerprinting technique requires high-quality genomic DNA, which is not only difficult to prepare but also requires culturing of the organism, resulting in a long turnaround time. In addition, fingerprint interpretation and matching can be complicated and require sophisticated computer software for large-scale analysis.

In contrast, nucleic acid amplification-based assays do not require culturing of the organisms, allowing the analysis of samples in real time. In many PCR-based typing assays, the target DNA of interest is amplified and labeled by PCR, and the labeled products are hybridized to an array of immobilized diagnostic probes. This method has been successfully used for the detection of mutations in drug resistance genes of Mycobacterium tuberculosis, and for Mycobacterium species identification. Spoligotyping, a reverse dot

blot assay that detects the presence of a series of unique spacers in the direct repeat (DR) locus, meets the need for a simple and rapid method by which to distinguish M. tuberculosis complex strains. However, spoligotyping has significantly less discriminatory power than fingerprinting.

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12.3E: Nucleic Acid Sequencing and rRNA Analysis

Nucleic acid sequencing and rRNA analysis consist of comparing nitrogen bases in rRNA.

Learning Objectives

- Describe how the 16SrRNA gene can be used for phylogenetic studies and in medical microbiology for bacterial identification

Key Points

- This method is effective in identifying general group differences of pathogens.
- 16S rRNA gene sequences contain hypervariable regions that can provide species -specific signature sequences useful for bacterial identification.
- This method can also be fine-tuned to identify pathogens at the species level.

Key Terms

- **ribosomes**: Large and complex molecular machine, found within all living cells, that serves as the primary site of biological protein synthesis.

Sixteen S ribosomal RNA (or 16S rRNA) is a component of the 30S small subunit of prokaryotic ribosomes. It is approximately 1.5kb (or 1500 nucleotides) in length. The genes coding for it are referred to as 16S rDNA, and are used in reconstructing phylogenies. Multiple sequences of 16S rRNA can exist within a single bacterium.

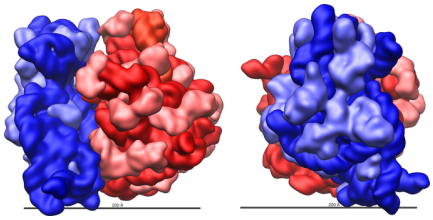

Figure: **Ribosomal RNA**: Structure and shape of the E.coli 70S ribosome. The large 50S ribosomal subunit (red) and small 30S ribosomal subunit (blue) are shown with a 200 Ångstrom (20 nm) scale bar. For the 50S subunit, the 23S (dark red) and 5S (orange red) rRNAs and the ribosomal proteins (pink) are shown. For the 30S subunit, the 16S rRNA (dark blue) and the ribosomal proteins (light blue) are shown.

The 16SrRNA gene is used for phylogenetic studies, as it is highly conserved between different species of bacteria and archaea. Carl Woese pioneered this use of 16S rRNA. In addition, mitochondrial and chloroplastic rRNA are also amplified. Unfortunately, while primers can be defined to amplify this gene from single genomes, this method is not accurate enough to estimate the diversity of microbial communities from their environments. Principal limits are the lack of real universal primers; DNA amplification biases and reference database selection impact the annotation of reads.

Paradoxically, methodological denial is now a rule in published articles that use 16S rRNA gene amplicon surveys to study unknown microbial communities. In these articles, one pair of primers (although many of them are designed, and provide different results) is used to amplify a region of the 16S rRNA gene. In addition to highly conserved primer binding sites, 16S rRNA gene sequences contain hypervariable regions that can provide species-specific signature sequences useful for bacterial identification. As a result, 16S rRNA gene sequencing has become prevalent in medical microbiology as a rapid and cheap (while inaccurate) alternative to phenotypic methods of bacterial identification. Although it was originally used to identify bacteria, 16S sequencing was subsequently found to be capable of reclassifying bacteria into completely new species, or even genera. It has also been used to describe new species that have never been successfully cultured.

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SECTION OVERVIEW

12.4: Immunity Disorders: Hypersensitivity

Topic hierarchy

12.4A: Type I (Anaphylactic) Reactions

12.4B: Diagnosis and Treatment of Allergy

12.4C: Type II (Cytotoxic) Reactions

12.4D: Type III (Immune Complex) Reactions

12.4E: Type IV (Delayed Cell-Mediated) Reactions

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12.4A: Type I (Anaphylactic) Reactions

Type I (or immediate/anaphylactic) hypersensitivity can be caused by the body's response to a foreign substance.

Learning Objectives

- Describe Type I hypersensitivity reactions

Key Points

- Common triggers for anaphylaxis include venom from insect bites or stings, foods, and medication.
- People with atopic diseases such as asthma, eczema, or allergic rhinitis have a high risk of anaphylaxis from food, latex, and radiocontrast agents.
- Anaphylaxis is a severe allergic reaction that starts suddenly and affects many body systems due to the release of inflammatory mediators and cytokines from mast cells and basophils.

Key Terms

- **anaphylaxis**: A severe and rapid systemic allergic reaction to an allergen, causing a constriction of the trachea, preventing breathing; anaphylactic shock.
- **hives**: Itchy, swollen, red areas of the skin which can appear quickly in response to an allergen or due to other conditions.
- **mast cells**: A mast cell is a resident cell of several types of tissues and contains many granules rich in histamine and heparin. Mat cells play a role in allergy, anaphylaxis, wound healing and defense against pathogens.

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. Anaphylaxis typically produces many different symptoms over minutes or hours. Symptoms typically include raised bumps on the skin (; hives), itchiness, red face or skin (flushing), or swollen lips.



Figure: **Hives and flushing on the back of a person with anaphylaxis**: Hives and flushing on the back of a person with anaphylaxis

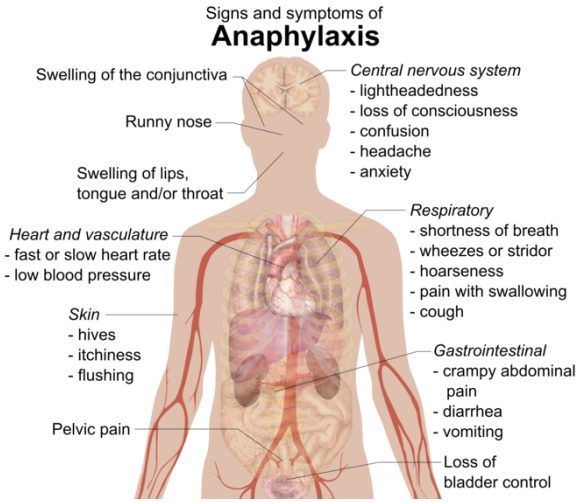

Figure: **Anaphylaxis**: A representation of the signs and symptoms of anaphylaxis that result from an allergic reaction.

Anaphylaxis can be caused by the body's response to almost any foreign substance. Common triggers include venom from insect bites or stings, foods, and medication. Foods are the most common trigger in children and young adults. Medications and insect bites and stings are more common triggers in older adults. Less common causes include physical factors, biological agents (such as semen), latex, hormonal changes, food additives (e.g. monosodium glutamate (MSG) and food coloring), and medications that are applied to the skin (topical medications). Exercise or temperature (either hot or cold) may also trigger anaphylaxis by causing tissue cells known as mast cells to release chemicals that start the allergic reaction.

Anaphylaxis caused by exercise is often also linked to eating certain foods. If anaphylaxis occurs while a person is receiving anesthesia, the most common causes are certain medications that are given to produce paralysis (neuromuscular blocking agents), antibiotics, and latex. Many foods can trigger anaphylaxis, even when the food is eaten for the first time. In Western cultures, the most common causes are eating or being in contact with peanuts, wheat, tree nuts, shellfish, fish, milk, and eggs.

People with atopic diseases such as asthma, eczema, or allergic rhinitis have a high risk of anaphylaxis from food, latex, and radiocontrast agents. These people do not have a higher risk from injectable medications or stings. People who have disorders caused by too many mast cells in their tissues (mastocytosis) or who are wealthier are at increased risk. The longer the time since the last exposure to an agent that caused anaphylaxis, the lower the risk of a new reaction.

Anaphylaxis is a severe allergic reaction that starts suddenly and affects many body systems. It results from the release of inflammatory mediators and cytokines from mast cells and basophils. This release is typically associated with an immune system reaction, but may also be caused by damage to cells that are not related to an immune reaction. When anaphylaxis is caused by an immune response, immunoglobulin E (IgE) binds to the foreign material that starts the allergic reaction (the antigen). The combination of IgE bound to the antigen activates FcεRI receptors on mast cells and basophils. The mast cells and basophils react by releasing inflammatory mediators such as histamine. These mediators increase the contraction of bronchial smooth muscles, cause blood vessels to widen (vasodilation), increase the leakage of fluid from blood vessels, and depress the actions of the heart muscle. There is also an immunologic mechanism that does not rely on IgE, but it is not known if this occurs in humans. When anaphylaxis is not caused by in immune response, the reaction is due to an agent that directly damages mast cells and basophils, causing them to release histamine and other substances that are usually associated with an allergic reaction (degranulation). Agents that can damage these cells include contrast medium for X-rays, opioids, temperature (hot or cold), and vibration.

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12.4B: Diagnosis and Treatment of Allergy

Allergy testing can help confirm or rule out allergies, reducing adverse reactions and limiting unnecessary avoidance and medications.

Learning Objectives

- Describe how the skin prick test and the allergy blood test work to assess the presence of allergen specific antibodies in an individual

Key Points

- To assess the presence of allergen -specific IgE antibodies, you can use one of two methods: a skin-prick test or an allergy blood test.
- Challenge testing is when small amounts of a suspected allergen are introduced to the body orally, through inhalation, or via other routes.
- Patch testing is used to help ascertain the cause of skin contact allergy (contact dermatitis).
- Traditional treatment and management of allergies consisted of simply avoiding the allergen in question.
- Several antagonistic drugs are used to block the action of allergic mediators or to prevent activation of cells and degranulation processes.

Key Terms

- **allergen**: a substance that causes an allergic reaction
- **antihistamine**: a drug or substance that counteracts the effects of a histamine. Commonly used to alleviate the symptoms of hay fever and other allergies
- **skin prick test**: Skin-prick testing is also known as “puncture testing” and “prick testing” because of the series of tiny punctures or pricks made in the patient’s skin. Small amounts of suspected allergens or their extracts (pollen, grass, mite proteins, peanut extract, etc.) are introduced to sites on the skin marked with pen or dye.

Allergy testing can help confirm or rule out allergies, reducing adverse reactions and limiting unnecessary avoidance and medications. Correct diagnosis, counseling, and avoidance advice based on valid allergy test results will help reduce the incidence of symptoms and medications and will improve quality of life. Earlier and more accurate diagnoses save costs due to a reduction in consultations, referrals to secondary care, misdiagnoses, and emergency admissions.

For assessing the presence of allergen-specific IgE antibodies, you can use two different methods: a skin prick test or an allergy blood test. Both methods are recommended by the NIH guidelines, are equally cost-effective, and have similar diagnostic value in terms of sensitivity and specificity. A healthcare provider can use the test results to identify the specific allergic triggers that may be contributing to symptoms.



Figure: **Allergy Skin Testing**: Skin testing on an arm.

Allergies undergo dynamic changes over time. Regular allergy testing for relevant allergens provides information on if and how patient management can be changed in order to improve health and quality of life. Annual testing is often the practice for determining whether allergies to milk, eggs, soy, and wheat have been outgrown. The testing interval is extended to two to three

years for allergies to peanuts, tree nuts, fish, and crustacean shellfish. Results of followup testing can guide decision-making regarding whether and when it is safe to introduce or re-introduce allergenic food into the diet.

Skin testing is also known as “puncture testing” and “prick testing” because of the series of tiny punctures or pricks made in the patient’s skin. Small amounts of suspected allergens or their extracts are introduced to sites on the skin marked with pen or dye (the dye should be carefully selected, lest it cause an allergic response itself). Sometimes, the allergens are injected “intradermally” into the patient’s skin with a needle and syringe. Common areas for testing include the inside forearm and the back. If the patient is allergic to the substance, then a visible inflammatory reaction will usually occur within 30 minutes. This response will range from a slight reddening of the skin to a full-blown hive (called “wheal and flare”) similar to a mosquito bite in more sensitive patients. Interpretation of the results of the skin-prick test is normally done by allergists on a scale of severity, with +/- meaning borderline reactivity and 4+ indicating a severe reaction.

In contrast, an allergy blood test is quick and simple and can be performed irrespective of age, skin condition, medication, symptom, disease activity, and pregnancy. In addition, multiple allergens can be detected with a single blood sample. Allergy blood tests are very safe, since the patient is not exposed to any allergens during the testing procedure. The test measures the concentration of specific IgE antibodies in the blood.

Challenge testing is when small amounts of a suspected allergen are introduced to the body orally, through inhalation, or via other routes. Challenge tests are utilized most often with foods or medicines. If the patient experiences significant improvement while avoiding a suspected allergen, she may then be “challenged” by reintroducing it to see if symptoms can be reproduced.

Patch testing is used to help ascertain the cause of skin contact allergy (contact dermatitis). Adhesive patches, usually treated with a number of different commonly allergenic chemicals or skin sensitizers, are applied to the back. The skin is then examined for possible local reactions at least twice, usually 48 hours after application and then again two or three days later.

Traditional treatment and management of allergies consisted of simply avoiding the allergen in question. However, while avoidance of allergens may reduce symptoms and avoid life-threatening anaphylaxis, it is difficult to do for those with allergies to pollen or other airborne allergens. Several antagonistic drugs are used to block the action of allergic mediators or to prevent activation of cells and degranulation processes. These include antihistamines, glucocorticoids, epinephrine (adrenaline), theophylline, and cromolyn sodium.

Desensitization or hyposensitization is a treatment in which the patient is gradually vaccinated with progressively larger doses of the allergen in question. This can either reduce the severity or eliminate hypersensitivity altogether. It relies on the progressive skewing of IgG antibody production to block excessive IgE production seen in atopys. In effect, the person builds up immunity to increasing amounts of the allergen. Studies have demonstrated the long-term efficacy and the preventive effect of immunotherapy in reducing the development of new allergies. A second form of immunotherapy involves the intravenous injection of monoclonal anti-IgE antibodies. These bind to free- and B cell-associated IgE, signaling their destruction.

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12.4C: Type II (Cytotoxic) Reactions

In type II (cytotoxic) hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.

Learning Objectives

- Describe Type II hypersensitivity reactions

Key Points

- The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen).
- Mediators of acute inflammation are generated at the site where a foreign antigen is recognized and membrane attack complexes cause cell lysis and death.
- In antibody -dependent cell-mediated cytotoxicity (ADCC), cells exhibiting the foreign antigen are tagged with antibodies (IgG or IgM) and they are then recognised by natural killer (NK) cells and macrophages which in turn kill these tagged cells.

Key Terms

- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **dendritic cells**: Dendritic cells are immune cells that function to process antigen material and present it on the surface of other cells of the immune system. They act as messengers between innate and adaptive immunity.
- **cytotoxic hypersensitivity**: In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.

In type II hypersensitivity (or cytotoxic hypersensitivity), the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces. The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen). These cells are recognized by macrophages or dendritic cells, which act as antigen-presenting cells. This causes a B cell response, wherein antibodies are produced against the foreign antigen.

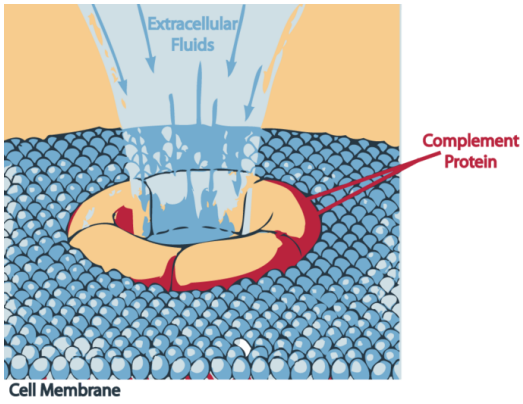

Figure: **Complement death**: A complement protein attacking an invader.

An example of type II hypersensitivity is the reaction to penicillin wherein the drug can bind to red blood cells, causing them to be recognized as different; B cell proliferation will take place and antibodies to the drug are produced. IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation to eliminate cells presenting foreign antigens (which are usually, but not in this case, pathogens). That is, mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death. The reaction takes hours to a day. The membrane attack complex (MAC;) is typically formed on the surface of pathogenic bacterial cells as a result of the activation of the alternative pathway and the classical pathway of the complement system, and it is one of the effector proteins of the immune system. The membrane-attack complex (MAC) forms transmembrane channels. These channels disrupt the phospholipid bilayer of target cells, leading to cell lysis and death.

Another form of type II hypersensitivity is called antibody-dependent cell-mediated cytotoxicity (ADCC). Here, cells exhibiting the foreign antigen are tagged with antibodies (IgG or IgM). These tagged cells are then recognised by natural killer (NK) cells and

macrophages (recognised via IgG bound (via the Fc region) to the effector cell surface receptor, CD16 (FcγRIII)), which in turn kill these tagged cells.

Autoimmune diseases resemble type II-IV hypersensitivity reactions. They differ from hypersensitivity reactions in that the antigens driving the immune process are self-antigens rather than non-self as in hypersensitivity reactions. Below are some examples of Type II hypersensitivity-like autoimmunity.

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12.4D: Type III (Immune Complex) Reactions

Type III hypersensitivity occurs when there is little antibody and an excess of antigen, leading to the formation of small immune complexes.

Learning Objectives

- Describe Type III hypersensitivity reactions

Key Points

- It is characterized by solvent antigens that are not bound to cell surfaces (which is the case in type II hypersensitivity) but bind antibodies to form immune complexes of different sizes.
- Large complexes can be cleared by macrophages but small immune complexes cannot be cleared and they insert themselves into small blood vessels, joints, and glomeruli, causing symptoms.
- The cause of damage is as a result of the action of cleaved complement anaphylotoxins C3a and C5a, which, mediate the onset of the inflammatory response and eventual tissue damage.

Key Terms

- **glomerulonephritis**: A form of nephritis characterized by inflammation of the glomeruli
- **immune complex**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.
- **Arthus reaction**: The Arthus reaction is a type of local type III hypersensitivity reaction which involves the deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium) and glomeruli.

Type III hypersensitivity occurs when there is little antibody and an excess of antigen, leading to small immune complexes being formed that do not fix complement and are not cleared from the circulation. It is characterized by solvent antigens that are not bound to cell surfaces (which is the case in type II hypersensitivity). When these antigens bind antibodies, immune complexes of different sizes form. Large complexes can be cleared by macrophages but macrophages have difficulty in the disposal of small immune complexes. These immune complexes insert themselves into small blood vessels, joints, and glomeruli, causing symptoms. Unlike the free variant, small immune complex bound to sites of deposition (like blood vessel walls) are far more capable of interacting with complement. These medium-sized complexes, formed in the slight excess of antigen, are viewed as being highly pathogenic.

Such depositions in tissues often induce an inflammatory response, and can cause damage wherever they precipitate. The cause of damage is as a result of the action of cleaved complement anaphylotoxins C3a and C5a, which, respectively, mediate the induction of granule release from mast cells (from which histamine can cause urticaria), and recruitment of inflammatory cells into the tissue (mainly those with lysosomal action, leading to tissue damage through frustrated phagocytosis by polymorphonuclear neutrophils and macrophages).

Immune complex glomerulonephritis, as seen in Henoch-Schönlein purpura is an example of IgA involvement in a nephropathy. The reaction can take hours, days, or even weeks to develop, depending on whether or not there is immunlogic memory of the precipitating antigen. Typically, clinical features emerge a week following initial antigen challenge, when the deposited immune complexes can precipitate an inflammatory response. Because of the nature of the antibody aggregation, tissues that are associated with blood filtration at considerable osmotic and hydrostatic gradient (e.g. sites of urinary and synovial fluid formation, kidney glomeruli and joint tissues respectively) bear the brunt of the damage. Hence, vasculitis, glomerulonephritis and arthritis are commonly-associated conditions as a result of type III hypersensitivity responses. As observed under methods of histopathology, acute necrotizing vasculitis within the affected tissues is observed concomitant to neutrophilic infiltration, along with notable eosinophilic deposition (fibrinoid necrosis).

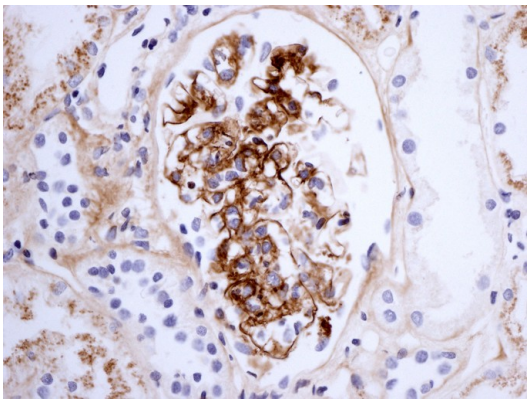

Figure: **Henoch-Schönlein nephritis IgA immunostaining**: Immune Complex Glomerulonephritis, as seen in Henoch-Schönlein purpura; this is an example of IgA involvement in a nephropathy.

Often, immunofluorescence microscopy can be used to visualize the immune complexes. Skin response to a hypersensitivity of this type is referred to as an Arthus reaction, and is characterized by local erythema and some induration. Platelet aggregation, especially in microvasculature, can cause localized clot formation, leading to blotchy hemorrhages. This typifies the response to injection of foreign antigen sufficient to lead to the condition of serum sickness. An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody, is referred to as a singular immune complex. After an antigen-antibody reaction, the immune complexes can be subject to any of a number of responses, including complement deposition, opsonization, phagocytosis, or processing by proteases.

Red blood cells carrying CR1-receptors on their surface may bind C3b-decorated immune complexes and transport them to phagocytes, mostly in liver and spleen, and return back to the general circulation. Immune complexes may themselves cause disease when they are deposited in organs, e.g. in certain forms of vasculitis. This is the third form of hypersensitivity in the Gell-Coombs classification, called Type III hypersensitivity. Immune complex deposition is a prominent feature of several autoimmune diseases, including systemic lupus erythematosus, cryoglobulinemia, rheumatoid arthritis, scleroderma and Sjögren's syndrome.

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12.4E: Type IV (Delayed Cell-Mediated) Reactions

Type IV hypersensitivity reactions are cell-mediated and take 2 to 3 days to develop.

Learning Objectives

- Describe Type IV cell-mediated reactions and explain why they take two to three days to develop

Key Points

- Cell-mediated immunity is an immune response that does not involve antibodies but rather involves the activation of phagocytes, natural killer cells (NK), antigen -specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
- In type IV hypersensitivity reactions, CD4+ helper T cells recognize antigen in a complex with Class 2 major histocompatibility complex on macrophages (the antigen-presenting cells).
- A classic example of delayed type IV hypersensitivity is the Mantoux tuberculin test in which skin induration indicates exposure to tuberculosis.

Key Terms

- **cellular immunity**: Cellular immunity protects the body by: activating antigen-specific cytotoxic T-lymphocytes, activating macrophages and natural killer cells and stimulating cytokine secretion to stimulate other cells involved in adaptive immune responses and innate immune responses.
- **type IV hypersensitivity**: A cell-mediated immune response that takes two to three days to develop.

Cell-mediated immunity is an immune response that does not involve antibodies, but rather involves the activation of phagocytes, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Historically, the immune system was separated into two branches: humoral immunity, for which the protective function of immunization could be found in the humor (cell-free bodily fluid or serum) and cellular immunity, for which the protective function of immunization was associated with cells. CD4 cells or helper T cells provide protection against different pathogens. Cytotoxic T cells cause death by apoptosis without using cytokines. Therefore in cell mediated immunity cytokines are not always present.

Cellular immunity protects the body by:

1. activating antigen-specific cytotoxic T-lymphocytes that are able to induce apoptosis in body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens

2. activating macrophages and natural killer cells, enabling them to destroy pathogens

3. stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses

Cell-mediated immunity is directed primarily at microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in removing virus-infected cells, but also participates in defending against fungi, protozoans, cancers, and intracellular bacteria. It also plays a major role in transplant rejection.

Type IV hypersensitivity is often called delayed type hypersensitivity as the reaction takes two to three days to develop. Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response. CD4+ helper T cells recognize antigen in a complex with Class 2 major histocompatibility complex. The antigen-presenting cells in this case are macrophages that secrete IL-12, which stimulates the proliferation of further CD4+ Th1 cells. CD4+ T cells secrete IL-2 and interferon gamma, further inducing the release of other Th1 cytokines, thus mediating the immune response. Activated CD8+ T cells destroy target cells on contact, whereas activated macrophages produce hydrolytic enzymes and, on presentation with certain intracellular pathogens, transform into multinucleated giant cells.

A classic example of delayed type IV hypersensitivity is the Mantoux tuberculin test in which skin induration indicates exposure to tuberculosis. Other examples include: temporal arteritis, Hashimoto's thyroiditis, symptoms of leprosy, symptoms of tuberculosis, coeliac disease, graft-versus-host disease and chronic transplant rejection.



Figure: **Mantoux test**: The reaction is read by measuring the diameter of induration (palpable raised, hardened area) across the forearm (perpendicular to the long axis) in millimeters. If there is no induration, the result should be recorded as “0 mm”. Erythema (redness) should not be measured. If a person has had a history of a positive tuberculin skin test, or had a recent tuberculin skin test (within one year), another skin test should be used.



Figure: **Mantoux tuberculin test**: The Mantoux test (also known as the Mantoux screening test, tuberculin sensitivity test, Pirquet test, or PPD test for purified protein derivative) is a diagnostic tool for tuberculosis. A standard dose of tuberculin is injected intradermally (between the layers of dermis) and read 48 to 72 hours later.

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SECTION OVERVIEW

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12.5B: The Roles of Genetics and Gender in Autoimmune Disease

12.5C: Cytotoxic Autoimmune Reactions

12.5D: Immune Complex Autoimmune Reactions

12.5E: Cell-Mediated Autoimmune Reactions

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12.5A: Immunodeficiency

Immunodeficiency occurs when the immune system cannot appropriately respond to infections.

Learning Objectives

- Explain the problems associated with immunodeficiency

Key Points

- If a pathogen is allowed to proliferate to certain levels, the immune system can become overwhelmed; immunodeficiency occurs when the immune system fails to respond sufficiently to a pathogen.
- Immunodeficiency can be caused by many factors, including certain pathogens, malnutrition, chemical exposure, radiation exposure, or even extreme stress.
- HIV is a virus that causes immunodeficiency by infecting helper T cells, causing cytotoxic T cells to destroy them.

Key Terms

- **phagocyte**: a cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria, and waste materials
- **lysis**: the disintegration or destruction of cells
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold to replicate or proliferate to high enough levels that the immune system becomes overwhelmed, leading to immunodeficiency; it may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or, possibly, by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes, elevating an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

HIV/AIDS

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system. The person has a high probability of becoming infected, including from opportunistic infections and tumors that do not usually affect people who have working immune systems.

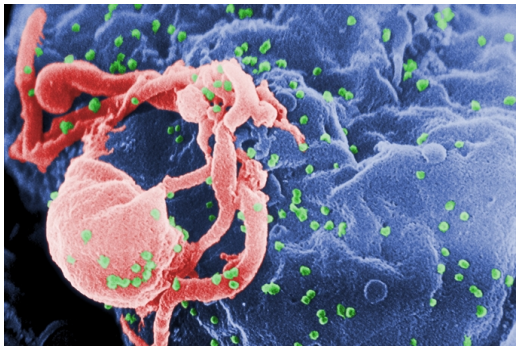

Figure: **Image of HIV: scanning electron micrograph of HIV-1 budding (in green, color added) from cultured lymphocyte**: Multiple round bumps on cell surface represent sites of assembly and budding of HIV. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells, cells that are or will become helper T cells. The acute viremia, or spreading of the virus, is almost invariably associated with activation of CD8+ T cells (which kill HIV-infected cells) and, subsequently, with antibody production. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

Ultimately, HIV causes AIDS by depleting CD4+ T cells (helper T cells). This weakens the immune system, allowing opportunistic infections. T cells are essential to the immune response; without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis (programmed cell death) may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

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12.5B: The Roles of Genetics and Gender in Autoimmune Disease

Autoimmunity is the failure of an organism in recognizing “self” which results in an immune response against its own cells and tissues.

Learning Objectives

- Define autoimmunity and explain how it gives rise to autoimmune disease

Key Points

- Autoimmune diseases are very often treated with steroids which will dampen the immune response.
- Certain individuals are genetically susceptible to developing autoimmune diseases and susceptibility is linked to immunoglobulin, T-cell receptor, and MHC complex genes.
- Women are more likely than men to develop an autoimmune disease, but the severity of the disease is more accentuated in men.

Key Terms

- **autoimmunity**: The condition where one’s immune system attacks one’s own tissues, i.e., an autoimmune disorder.
- **alloimmunity**: Immunity, obtained from another, against one’s own cells.

Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmunity is often caused by a lack of germ development of a target body and as such the immune response acts against its own cells and tissues. Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), Sarcoidosis, systemic lupus erythematosus (SLE), Sjögren’s syndrome, Churg-Strauss Syndrome, Hashimoto’s thyroiditis, Graves’ disease, idiopathic thrombocytopenic purpura, Addison’s Disease, rheumatoid arthritis (RA), and allergies.

Autoimmune diseases are very often treated with steroids. The misconception that an individual’s immune system is totally incapable of recognizing self antigens is not new. Paul Ehrlich, at the beginning of the 20th century, proposed the concept of horror autotoxicus, wherein a ‘normal’ body does not mount an immune response against its own tissues. Therefore, any autoimmune response was perceived to be abnormal and postulated to be connected with human disease. Now, it is accepted that autoimmune responses are an integral part of vertebrate immune systems (sometimes termed ‘natural autoimmunity’), normally prevented from causing disease by the phenomenon of immunological tolerance to self-antigens.

Autoimmunity should not be confused with alloimmunity. While a high level of autoimmunity is unhealthy, a low level of autoimmunity may actually be beneficial. First, low-level autoimmunity might aid in the recognition of neoplastic cells by CD8+ T cells, and thus reduce the incidence of cancer. Second, autoimmunity may have a role in allowing a rapid immune response in the early stages of an infection when the availability of foreign antigens limits the response (i.e., when there are few pathogens present).

Certain individuals are genetically susceptible to developing autoimmune diseases. This susceptibility is associated with multiple genes plus other risk factors. However, genetically predisposed individuals do not always develop autoimmune diseases. Three main sets of genes are suspected in many autoimmune diseases. These genes are related to immunoglobulins, T-cell receptors, and the major histocompatibility complexes (MHC). Immunoglobulins and T-cell receptors are involved in the recognition of antigens and they are inherently variable and susceptible to recombination. These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of self-reactivity. Scientists such as H. McDevitt, G. Nepom, J. Bell, and J. Todd have also provided strong evidence to suggest that certain MHC class II allotypes are strongly correlated with disease. For example:

1. HLA DR2 is strongly positively correlated with Systemic Lupus Erythematosus, narcolepsy and multiple sclerosis, and negatively correlated with DM Type 1.

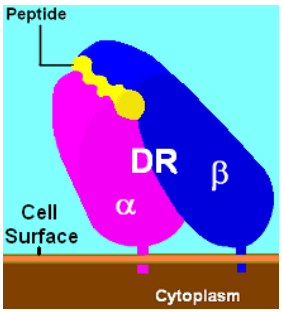

Figure: **MHC Class II, DR**: HLA-DR is a MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6 region 6p21.31. The complex of HLA-DR and its ligand, a peptide of 9 amino acids in length or longer, constitutes a ligand for the T-cell receptor (TCR).

2. HLA DR3 is correlated strongly with Sjögren's syndrome, myasthenia gravis, SLE, and DM Type 1.

3. HLA DR4 is correlated with the genesis of rheumatoid arthritis, Type 1 diabetes mellitus, and pemphigus vulgaris.

Fewer correlations exist with MHC class I molecules. The most notable and consistent is the association between HLA B27 and ankylosing spondylitis. Correlations may exist between polymorphisms within class II MHC promoters and autoimmune disease. The contributions of genes outside the MHC complex remain the subject of research, in animal models of disease (Linda Wicker's extensive genetic studies of diabetes in the NOD mouse), and in patients (Brian Kotzin's linkage analysis of susceptibility to SLE).

A person's sex also seems to have some role in the development of autoimmunity, classifying most autoimmune diseases as sex-related diseases. Nearly 75% of the more than 23.5 million Americans who suffer from autoimmune disease are women, although it is less-frequently acknowledged that millions of men also suffer from these diseases. However, autoimmune diseases that develop in men tend to be more severe. A few autoimmune diseases that men are just as or more likely to develop as women, include: ankylosing spondylitis, type 1 diabetes mellitus, Wegener's granulomatosis, and Crohn's disease. The reasons for the sex role in autoimmunity are unclear. However, women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. In addition, involvement of sex steroids is indicated by the fact that many autoimmune diseases tend to fluctuate in accordance with hormonal changes, for example, during pregnancy. Interestingly, a history of pregnancy also appears to leave a persistent increased risk for autoimmune disease. Indeed, it has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce autoimmunity. This would tip the gender balance in the direction of the female. Another theory suggests the female high tendency to get autoimmunity is due to an imbalanced X chromosome inactivation.

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12.5C: Cytotoxic Autoimmune Reactions

Autoimmunity is a result of the failure of an organism's immune system to recognize "self".

Learning Objectives

- Define autoimmunity and describe how it can lead to disease

Key Points

- Autoimmunity is often caused by a lack of germ development of a target body and, as such, the immune response acts against its own cells and tissues.
- Certain individuals are genetically susceptible to developing autoimmune diseases but genetically predisposed individuals do not always develop an autoimmune disease.
- Three main sets of genes are suspected in many autoimmune diseases: immunoglobulins, T-cell receptors and the major histocompatibility complexes (MHC).
- Women are more likely to develop an autoimmune disease.

Key Terms

- **alloimmunity**: Immunity, obtained from another, against one's own cells.
- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.

Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, creating an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an *autoimmune* disease.

Autoimmunity is often caused by a lack of germ development of a target body and, as such, the immune response acts against its own cells and tissues. Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), Sarcoidosis, systemic lupus erythematosus (SLE), Sjögren's syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, Addison's Disease, rheumatoid arthritis (RA) and allergies.

Autoimmune diseases are very often treated with steroids. The misconception that an individual's immune system is totally incapable of recognizing self antigens is not new. Paul Ehrlich, at the beginning of the twentieth century, proposed the concept of horror autotoxicus, wherein a 'normal' body does not mount an immune response against its own tissues. Thus, any autoimmune response was perceived to be abnormal and postulated to be connected with human disease. Now, it is accepted that autoimmune responses are an integral part of vertebrate immune systems (sometimes termed 'natural autoimmunity'), normally prevented from causing disease by the phenomenon of immunological tolerance to self-antigens.

Autoimmunity should not be confused with *alloimmunity*. Certain individuals are genetically susceptible to developing autoimmune diseases. This susceptibility is associated with multiple genes plus other risk factors. Genetically predisposed individuals do not always develop autoimmune diseases. Three main sets of genes are suspected in many autoimmune diseases: immunoglobulins, T-cell receptors and the major histocompatibility complexes (MHC).

Immunoglobulins and the T-cell receptors are involved in the recognition of antigens and they are inherently variable and susceptible to recombination. These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of self-reactivity. Scientists such as H. McDevitt, G. Nepom, J. Bell and J. Todd have also provided strong evidence to suggest that certain MHC class II allotypes are strongly correlated with autoimmunity.

For example:

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According to the American Autoimmune Related Diseases Association (AARDA), autoimmune diseases that develop in men tend to be more severe. A few autoimmune diseases that men are just as or more likely to develop as women, include: ankylosing spondylitis, type 1 diabetes mellitus, Wegener's granulomatosis, Crohn's disease, Primary sclerosing cholangitis and psoriasis.

The reasons for the sex role in autoimmunity are unclear. Women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. Similarly, involvement of sex steroids is indicated by the fact that many autoimmune diseases tend to fluctuate in accordance with hormonal changes. Interestingly, a history of pregnancy also appears to leave a persistent increased risk for autoimmune disease. Indeed, it has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce autoimmunity. This would tip the gender balance in the direction of the female.

Another theory suggests the female-high tendency to get autoimmunity is due to an imbalanced X chromosome inactivation. The X-inactivation skew theory, proposed by Princeton University's Jeff Stewart, has recently been confirmed experimentally in scleroderma and autoimmune thyroiditis.

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12.5D: Immune Complex Autoimmune Reactions

An immune complex is formed from the integral binding of an antibody to a soluble antigen and can function as an epitope.

Learning Objectives

- Describe how immune complex autoimmune reactions arise

Key Points

- After an antigen – antibody reaction, the immune complexes can be subject to any of a number of responses including complement deposition, opsonization, phagocytosis, or processing by proteases.
- Immune complexes may cause disease when they are deposited in organs.
- The Arthus reaction involves the in situ formation of antigen/antibody complexes after the intradermal injection of an antigen (as seen in passive immunity).

Key Terms

- **epitope**: That part of a biomolecule (such as a protein) that is the target of an immune response.
- **immune complex**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.

An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex. After an antigen-antibody reaction, the immune complexes can be subject to any of a number of responses, including complement deposition, opsonization, phagocytosis, or processing by proteases. Red blood cells carrying CR1-receptors on their surface may bind C3b-decorated immune complexes and transport them to phagocytes, mostly in liver and spleen, and return back to the general circulation. Immune complexes may cause disease when they are deposited in organs, e.g. in certain forms of vasculitis. This is the third form of hypersensitivity in the Gell-Coombs classification, called Type III hypersensitivity. Immune complex deposition is a prominent feature of several autoimmune diseases, including systemic lupus erythematosus, cryoglobulinemia, rheumatoid arthritis, scleroderma, and Sjögren's syndrome.

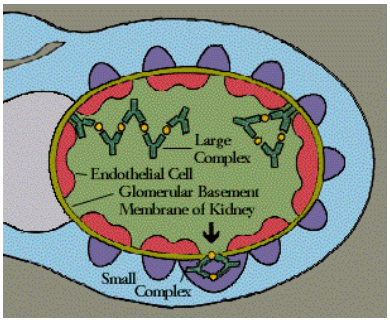

Figure: **Immune Complex Diseases**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.

In immunology, the Arthus reaction is a type of local type III hypersensitivity reaction. Type III hypersensitivity reactions are immune complex-mediated. They involve the deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium), and glomeruli. The Arthus reaction involves the in situformation of antigen/antibody complexes after the intradermal injection of an antigen (as seen in passive immunity). If the animal/patient was previously sensitized (has circulating antibody), an Arthus reaction occurs. Typical of most mechanisms of the type III hypersensitivity, Arthus manifests as local vasculitis due to deposition of IgG-based immune complexes in dermal blood vessels. Activation of complement primarily results in cleavage of soluble complement proteins forming C5a and C3a, which activate recruitment of PMNs and local mast cell degranulation (requiring the binding of the immune complex onto FcγRIII), resulting in an inflammatory response. Further aggregation of immune complex-related processes induces a local fibrinoid necrosis with ischemia-aggravating thrombosis in the tissue vessel walls. The end result is a localized area of redness and induration that typically lasts a day or so. Arthus reactions have been infrequently reported after vaccination against diphtheria and tetanus.

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12.5E: Cell-Mediated Autoimmune Reactions

Cell-mediated autoimmunity can happen by several mechanisms involving cells of the immune system and their receptors.

Learning Objectives

- Define cell-mediated autoimmunity and describe the mechanisms that are thought to operate in the pathogenesis of autoimmune disease

Key Points

- Superantigens can bypass the T-cell requirement for B cell activation.
- In some instances such as celiac disease, B cells can be activated to produce antibodies to epitope A by T cells activated by epitope B.
- Autoreactive B cells in spontaneous autoimmunity survive due to subversion both of the T cell help pathway and of the feedback signal through B cell receptor, leading to loss of the negative signals responsible for B cell self- tolerance without necessarily requiring loss of T cell self-tolerance.
- DQ therefore is involved in recognizing common self- antigens and presenting those antigens to the immune system in order to develop tolerance from a very young age.

Key Terms

- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.
- **tolerance**: The process by which the immune system does not attack an antigen

Several mechanisms are thought to be operative in the pathogenesis of autoimmune diseases, against a backdrop of genetic predisposition and environmental modulation. Four of the important mechanisms are described below.

T Cell Bypass

A normal immune system requires the activation of B cells by T cells before the former can produce antibodies in large quantities. This requirement of a T cell can be bypassed in rare instances, such as infection by organisms producing super-antigens, which are capable of initiating polyclonal activation of B cells, or even of T cells, by directly binding to the β-subunit of T cell receptors in a non-specific fashion.

T Cell to B Cell Discordance

A normal immune response is assumed to involve B and T cell responses to the same antigen, where B cells recognize conformations on the surface of a molecule for B cells, and T cells recognize pre-processed peptide fragments of proteins for T cells. However, there is no evidence that this response is required. All that is required is that a B cell that recognizes antigen X endocytoses processes a protein Y (normally =X) and presents it to a T cell. Roosnek and Lanzavecchia showed that B cells recognizing IgGFc could get help from any T cell that responds to an antigen co-endocytosed with IgG by the B cell as part of an immune complex. In coeliac disease it seems likely that B cells that recognize transglutamine tissue are helped by T cells that recognize gliadin.

Aberrant B Cell Receptor-Mediated Feedback

A feature of human autoimmune disease is that it is largely restricted to a small group of antigens, several of which have known signaling roles in the immune response (for example DNA, C1q, IgGFc, Ro, Con. A receptor, Peanut agglutinin receptor(PNAR)). This fact gave rise to the idea that spontaneous autoimmunity may result when the binding of antibody to certain antigens leads to aberrant signals being fed back to parent B cells through membrane bound ligands. These ligands include B cell receptor (for antigen), IgG Fc receptors, CD21 (which binds complement C3d), Toll-like receptors 9 and 7 (which can bind DNA and nucleoproteins) and PNAR. More indirect aberrant activation of B cells can also be envisaged with autoantibodies to acetyl choline receptor (on thymic myoid cells) and hormone binding proteins. Together with the concept of T cell-B cell discordance, this idea forms the basis of the hypothesis of self-perpetuating autoreactive B cells. Autoreactive B cells in spontaneous autoimmunity are seen as surviving because of subversion both of the T cell help pathway and of the feedback signal through the B cell receptor. This reaction thereby overcomes the negative signals responsible for B cell self-tolerance without necessarily requiring loss of T cell self-tolerance.

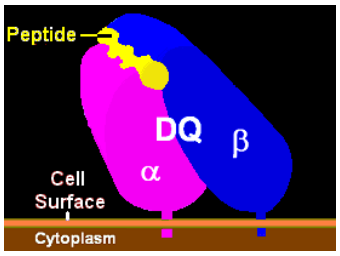

Figure: **MHC Class II, DQ**: HLA-DQ (DQ) is a cell surface receptor type protein found on antigen presenting cells (APC). DQ is an alpha-beta heterodimer of the MHC class II type.

Immune system cells called dendritic cells present antigens to active lymphocytes. Dendritic cells that are defective in apoptosis can lead to inappropriate systemic lymphocyte activation and consequent decline in self-tolerance.

HLA-DQ (DQ) is a cell surface receptor type protein found on antigen presenting cells. DQ is an α heterodimer of the MHC Class II type. The α and β chains are encoded by HLA-DQA1 and HLA-DQB1, respectively. These two loci are adjacent to each other on chromosome 6p21.3. Both the α-chain and β-chain vary greatly. A person often produces two α-chain and two β-chain variants and thus four DQ isoforms.

DQ isoforms can bind to and present foreign and self antigens to T-cells. In this process T-cells are stimulated to grow and can signal B-cells to produce antibodies. DQ therefore is involved in recognizing common self-antigens and presenting those antigens to the immune system in order to develop tolerance from a very young age. When tolerance to self proteins is lost, DQ may become involved in autoimmune disease. Two autoimmune diseases in which HLA-DQ is involved are celiac disease and diabetes mellitus type 1. DQ is one of several antigens involved in rejection of organ transplants. As a variable cell surface receptor on immune cells, these D antigens, originally HL-A4 antigens, are involved in graft versus host disease when lymphoid tissues are transplanted between people.

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SECTION OVERVIEW

12.6: Immunity Disorders: Immunodeficiencies

Topic hierarchy

12.6A: Primary Immunodeficiency Diseases

12.6B: Secondary Immunodeficiency Diseases

12.6C: Immunotherapy for Cancer

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12.6A: Primary Immunodeficiency Diseases

Primary immunodeficiencies are disorders in which part of the body's immune system is missing, or does not function properly.

Learning Objectives

- Describe primary immunodeficiency disorders and explain what treatment options are available

Key Points

- To be considered a primary immunodeficiency, the cause of the immune deficiency must not be secondary in nature (caused by other disease, drug treatment, or environmental exposure to toxins).
- Most primary immunodeficiencies are genetic disorders; the majority are diagnosed in children under the age of one, although milder forms may not be recognized until adulthood.
- The precise symptoms of a primary immunodeficiency depend on the type of defect but generally include recurrent or persistent infections or developmental delay as a result of infection.

Key Terms

- **genetic disorder**: An illness caused by abnormalities in genes or chromosomes, especially a condition that is present prior to birth. Most genetic disorders are quite rare and affect one person in every several thousands or millions.
- **immunodeficiency**: A depletion in the body's natural immune system, or in some component of it.

Primary immunodeficiencies are disorders in which a part of the body's immune system is missing or does not function properly. To be considered a primary immunodeficiency, the cause of the immune deficiency must not be secondary in nature (caused by another disease, drug treatment, or environmental exposure to toxins). Most primary immunodeficiencies are genetic disorders; the majority are diagnosed in children under the age of one, although milder forms may not be recognized until adulthood.

Symptoms

The precise symptoms of a primary immunodeficiency depend on the type of defect. Generally, the symptoms and signs that lead to the diagnosis of an immunodeficiency include recurrent or persistent infections, or developmental delay as a result of infection. Particular organ problems; such as diseases involving the skin, heart, facial development and skeletal system; may be present in certain conditions. Others predispose to autoimmune disease, where the immune system attacks the body's own tissues, or tumors (sometimes specific forms of cancer, such as lymphoma). The nature of the infections, as well as the additional features, may provide clues as to the exact nature of the immune defect.

Diagnostic Tests

The basic tests performed when an immunodeficiency is suspected should include a full blood count (including accurate lymphocyte and granulocyte counts) and immunoglobulin levels. Tthe three most important types of antibodies are IgG, IgA and IgM.

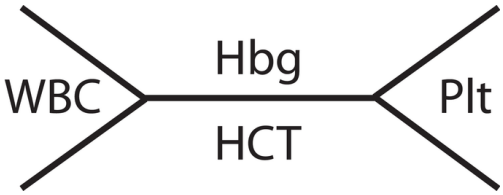

Figure: **Complete Blood Count**: Schematics (also called "fishbones") of shorthand commonly used by clinicians for complete blood count. The shorthand on the right is used more often in the U.S. Hgb=Hemoglobin, WBC=White blood cells, Plt=Platelets, Hct=Hematocrit.

Other tests are performed depending on the suspected disorder:

- Quantification of the different types of mononuclear cells in the blood (lymphocytes and monocytes): different groups of T lymphocytes (dependent on their cell surface markers, e.g. CD4+, CD8+, CD3+, TCRα and TCRγ); groups of B lymphocytes (CD19, CD20, CD21 and Immunoglobulin); natural killer cells and monocytes (CD15+); as well as activation markers (HLA-DR, CD25, CD80 (B cells)

- Tests for T cell function: skin tests for delayed-type hypersensitivity, cell responses to mitogens and allogeneic cells, cytokine production by cells
- Tests for B cell function: antibodies to routine immunizations and commonly acquired infections, quantification of IgG subclasses
- Tests for phagocyte function: reduction of nitro blue tetrazolium chloride, assays of chemotaxis, bactericidal activity

Due to the rarity of many primary immunodeficiencies, many of the above tests are highly specialized and tend to be performed in research laboratories.

Immunodeficiency Disorders

In genetic immunodeficiency disorders, both T lymphocytes and often B lymphocytes—regulators of adaptive immunity—are dysfunctional or decreased in number. The main members are various types of severe combined immunodeficiency (SCID).

In primary antibody deficiencies, one or more isotypes of immunoglobulin are decreased or don't function properly. These proteins, generated by plasma cells, normally bind to pathogens, targeting them for destruction.

A number of syndromes, including the following, escape formal classification but are otherwise recognisable by particular clinical or immunological features:

- Wiskott-Aldrich syndrome
- DNA repair defects not causing isolated SCID; for example ataxia telangiectasia and ataxia-like syndrome
- DiGeorge syndrome (when associated with thymic defects)
- Various immuno-osseous dysplasias (abnormal development of the skeleton with immune problems);for example, cartilage-hair hypoplasia, Schimke syndrome

In certain conditions, including the following, the regulation rather than the intrinsic activity of parts of the immune system is the predominant problem:

- Immunodeficiency with hypopigmentation or albinism; for example, Chediak-Higashi syndrome, Griscelli syndrome type two
- Familial hemophagocytic lymphohistiocytosis; for example, perforin deficiency, MUNC13D deficiency, syntaxin 11 deficiency
- X-linked lymphoproliferative syndrome

Phagocytes are the cells that engulf and ingest pathogens (phagocytosis), and destroy them with chemicals. Monocytes/macrophages as well as granulocytes are capable of this process. In certain conditions, either the number of phagocytes is reduced or their functional capacity is impaired. Several rare conditions are due to defects in the innate immune system, which is a basic line of defense independent of the more advanced lymphocyte-related systems. Many of these conditions are associated with skin problems.

Rather than predisposing for infections, most of the autoinflammatory disorders lead to excessive inflammation. Many manifest themselves as periodic fever syndromes. They may involve various organs directly, as well as predisposing for long-term damage by leading to amyloid deposition.

The complement system is part of the innate as well as the adaptive immune system; it is a group of circulating proteins that can bind pathogens and form a membrane attack complex. Complement deficiencies are the result of a lack of any of these proteins. They may predispose to infections but also to autoimmune conditions.

Treatment

The treatment of primary immunodeficiencies depends foremost on the nature of the abnormality. This may range from immunoglobulin replacement therapy in antibody deficiencies—in the form of intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG)—to hematopoietic stem cell transplantation for SCID and other severe immunodeficiences. SCID can now be treated with a bone marrow transplant. Reduction of exposure to pathogens may be recommended, and in many situations prophylactic antibiotics may be advised.

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12.6B: Secondary Immunodeficiency Diseases

Secondary immunodeficiencies refer to acquired immune system disorders.

Learning Objectives

- Define immunodeficiency and list the types that occur

Key Points

- A deficit in the immune system can lead to unusually severe or uncommon recurrent infections.
- Secondary immune deficiencies or acquired deficiencies, more frequent than primary immune deficiencies, are problems of the immune system that are not genetic and which are caused by external factors.
- Secondary immunodeficiency disorders can occur in, for example, malnutrition, aging, many types of cancer (such as leukemia, lymphoma, multiple myeloma), and certain chronic infections such as acquired immunodeficiency syndrome (AIDS).
- Immunosuppression is one form of secondary immunodeficiency performed to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases, such as rheumatoid arthritis or Crohn's disease.
- A person who is undergoing immunosuppression or whose immune system is weak for other reasons (for example, chemotherapy, HIV, and Lupus), is said to be immunocompromised.

Key Terms

- **immunodeficiency**: A depletion in the body's natural immune system, or in some component of it.
- **immunocompromised**: Having an immune system that has been impaired by disease or treatment.
- **immunosuppressive**: Having the capability to suppress the immune system, capable of immunosuppression.
- **secondary infection**: any infection that arises subsequent to a pre-existing infection; but especially a nosocomial infection

Immunodeficiency (or immune deficiency) is a state in which the immune system's ability to fight infectious disease is compromised or entirely absent. Immunodeficiency may also decrease cancer immunosurveillance. Most cases of immunodeficiency are acquired ("secondary") but some people are born with defects in their immune system, or primary immunodeficiency. Transplant patients take medications to suppress their immune system as an anti-rejection measure, as do some patients suffering from an over-active immune system. A person who has an immunodeficiency of any kind is said to be immunocompromised. An immunocompromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect everyone. Distinction between primary versus secondary immunodeficiencies are based on, respectively, whether the cause originates in the immune system itself or is, in turn, due to insufficiency of a supporting component of it or an external decreasing factor of it.

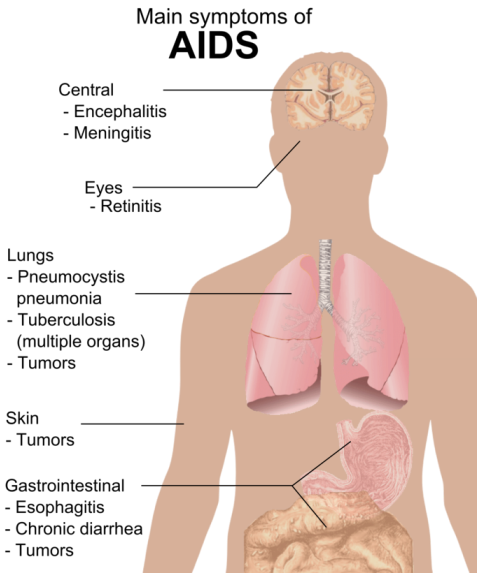

Figure: **Main Symptoms of AIDS**: Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half the people infected with HIV develop AIDS within 10 years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia and cachexia.

Primary Immunodeficiency (PID)

A number of rare diseases feature a heightened susceptibility to infections from childhood onward. Primary Immunodeficiency is also known as “congenital immunodeficiencies. ” Many of these disorders are hereditary and are autosomal recessive or X-linked. There are over 80 recognized primary immunodeficiency syndromes; they are generally grouped by the part of the immune system that is malfunctioning, such as lymphocytes or granulocytes. The treatment of primary immunodeficiencies depends on the nature of the defect and may involve antibody infusions, long-term antibiotics, and (in some cases) stem cell transplantation.

Secondary Immunodeficiencies

Secondary immunodeficiencies, also known as acquired immunodeficiencies, can result from various immunosuppressive agents, for example, malnutrition, aging and particular medications (e.g., chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids). For medications, the term immunosuppression generally refers to both beneficial and potential adverse effects of decreasing the function of the immune system, while the term immunodeficiency generally refers solely to the adverse effect of increased risk for infection. Many specific diseases directly or indirectly cause immunosuppression. This includes many types of cancer, particularly those of the bone marrow and blood cells (leukemia, lymphoma, multiple myeloma), and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV directly infects a small number of T helper cells and also impairs other immune system responses indirectly.

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12.6C: Immunotherapy for Cancer

Cancer immunotherapy is the use of the body's own immune system to reject cancer.

Learning Objectives

- Describe the use of immunotherapy in cancer treatment

Key Points

- Cancer immunotherapy can involve immunization of the patient with a cancer vaccine, administration of therapeutic antibodies as drugs, or cell-based immunotherapy.
- Vaccines can be raised against antigens that are inappropriate either for the cell type or for its environment.
- Adoptive cell-based immunotherapy involves isolating either allogenic or autologous immune cells, enriching them outside the body, and transfusing them back into the patient.
- Monoclonal antibodies can be raised against unusual antigens that are presented on the surfaces of tumors.

Key Terms

- **immunotherapy**: the treatment of cancer by improving the ability of the host to reject a tumor immunologically
- **allogenic**: genetically distinct, but of the same species
- **autologous**: derived from part of the same individual (i.e., from the recipient rather than the donor)

Cancer immunotherapy is the use of the body's own immune system to reject cancer. The main idea is stimulating the patient's immune system to attack the malignant tumor cells that are responsible for the disease. This can be either through immunization of the patient (e.g., by administering a cancer vaccine such as Dendreon's Provenge), in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed, or through the administration of therapeutic antibodies as drugs, in which case the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies. Cell-based immunotherapy is another major entity of cancer immunotherapy. This involves immune cells such as the natural killer cells (NK cells), lymphokine-activated killer cells (LAK cells), cytotoxic T lymphocytes (CTLs), and dendritic cells (DC). These immune cells are either activated *in vivo* by administering certain cytokines such as interleukins, or they are isolated, enriched, and transfused back into the patient to fight against cancer.

Since the immune system responds to the environmental factors it encounters on the basis of discrimination between self and non-self, many kinds of tumor cells that arise as a result of the onset of cancer are more or less tolerated by the patient's own immune system since the tumor cells are essentially the patient's own cells that are growing, dividing, and spreading without proper regulatory control. In spite of this fact, however, many kinds of tumor cells display unusual antigens that are inappropriate for either the cell type or its environment or that are only normally present during the organism 's development (e.g. fetal antigens). Examples of such antigens include the glycosphingolipid GD2, a disialoganglioside that is normally only expressed at a significant level on the outer surface membranes of neuronal cells, where its exposure to the immune system is limited by the blood-brain barrier.

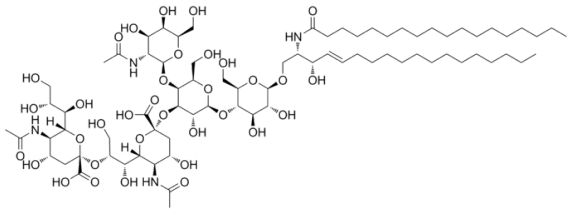

Figure: **Structure of GD2**: GD2 is a disialoganglioside expressed on tumors of neuroectodermal origin, including human neuroblastomas and melanomas, with highly restricted expression on normal tissues, principally to the cerebellum and peripheral nerves in humans. The relatively tumor-specific expression of GD2 makes it a suitable target for immunotherapy with monoclonal antibodies or with artificial T-cell receptors.

GD2 is expressed on the surfaces of a wide range of tumor cells, including neuroblastomas, medulloblastomas, astrocytomas, melanomas, small-cell lung cancer, osteosarcomas, and other soft tissue sarcomas. GD2 is thus a convenient tumor-specific target for immunotherapies.

Adoptive cell-based immunotherapy involves isolating either allogenic or autologous immune cells, enriching them outside the body, and transfusing them back to the patient. The injected immune cells are highly cytotoxic to the cancer cells and so help to

fight them.

Antibodies are a key component of the adaptive immune response. They play a central role in both the recognition of foreign antigens and the stimulation of an immune response to them. It is not surprising, therefore, that many immunotherapeutic approaches involve the use of antibodies. The advent of monoclonal antibody technology has made it possible to raise antibodies against specific antigens, such as the unusual antigens that are presented on the surfaces of tumors. A number of therapeutic monoclonal antibodies have been approved for use in humans, such as alemtuzumab, an anti-CD52 humanized IgG1 monoclonal antibody indicated for the treatment of chronic lymphocytic leukemia (CLL). Radioimmunotherapy in turn involves the use of radioactively conjugated murine antibodies against cellular antigens, mostly for treatment of lymphomas.

The development and testing of second-generation immunotherapies is already under way. While antibodies targeted to disease-causing antigens can be effective under certain circumstances, in many cases their efficacy may be limited by other factors. In the case of cancer tumors, the microenvironment is immunosuppressive, allowing even those tumors that present unusual antigens to survive and flourish in spite of the immune response generated by the cancer patient against his own tumor tissue. Certain members of a group of molecules known as cytokines, such as interleukin-2, also play a key role in modulating the immune response. Cytokines have been tested in conjunction with antibodies in order to generate an even more devastating immune response against the tumor. While the therapeutic administration of such cytokines may cause systemic inflammation, resulting in serious side effects and toxicity, there is a new generation of chimeric molecules consisting of an immune-stimulatory cytokine attached to an antibody that targets a tumor. These chimeric molecules are able to generate a very effective yet localized immune response against the tumor tissue, destroying the cancer-causing cells without the unwanted side effects.

Dermatologists use new creams and injections in the management of benign and malignant skin tumors. Topical immunotherapy utilizes an immune enhancement cream (imiquimod), which is an interferon producer, causing the patient's own killer T cells to destroy warts, actinic keratoses, basal cell carcinoma, squamous cell carcinoma, cutaneous T cell lymphoma, and superficial spreading melanoma. Injection immunotherapy uses mumps, candida, or trichophytin antigen injections to treat warts (HPV-induced tumors).

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CHAPTER OVERVIEW

13: Antimicrobial Drugs

An antimicrobial is an agent that kills microorganisms or stops their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungals are used against fungi

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- 13.1B: Antibiotic Discovery
- 13.1C: Antibiotics and Selective Toxicity
- 13.1D: Spectrum of Antimicrobial Activity
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Thumbnail: Staphylococcus aureus - Antibiotics Test plate. (Public Domain; CDC / Provider: Don Stalons).

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SECTION OVERVIEW

13.1: Overview of Antimicrobial Therapy

Topic hierarchy

13.1A: Origins of Antimicrobial Drugs

13.1B: Antibiotic Discovery

13.1C: Antibiotics and Selective Toxicity

13.1D: Spectrum of Antimicrobial Activity

13.1E: Antibiotic Classifications

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13.1A: Origins of Antimicrobial Drugs

The era of antimicrobials begins when Pasteur and Joubert discover that one type of bacteria could prevent the growth of another.

Learning Objectives

- Recall the technical defintion of antibiotics

Key Points

- Antibiotics are only those substances that are produced by one microorganism that kill, or prevent the growth, of another microorganism.
- In today's common usage, the term antibiotic is used to refer to almost any drug that attempts to rid your body of a bacterial infection.
- The discovery of antimicrobials like penicillin and tetracycline paved the way for better health for millions around the world.

Key Terms

- **antimicrobial**: An agent that destroys microbes, inhibits their growth, or prevents or counteracts their pathogenic action.
- **penicillin**: Any of a group of broad-spectrum antibiotics obtained from Penicillium molds or synthesized; they have a beta-lactam structure; most are active against gram-positive bacteria and used in the treatment of various infections and diseases.

The history of antimicrobials begins with the observations of Pasteur and Koch, who discovered that one type of bacteria could prevent the growth of another. They did not know at that time that the reason one bacterium failed to grow was that the other bacterium was producing an antibiotic. Technically, antibiotics are only those substances that are produced by one microorganism that kill, or prevent the growth, of another microorganism.

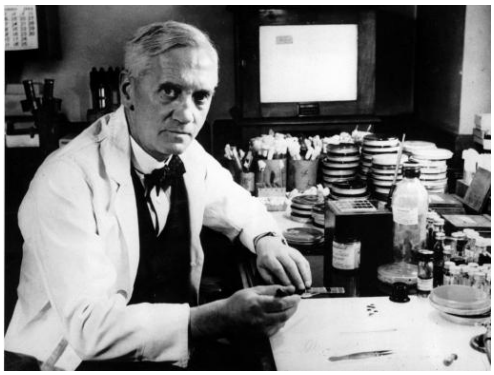

Figure: **Alexander Fleming**: In 1928 Alexander Fleming observed antibiosis against bacteria by a fungus of the genus Penicillium and postulated the effect was mediated by an antibacterial compound, penicillin, and that its antibacterial properties could be exploited for chemotherapy.

The discovery of antimicrobials like penicillin by Alexander Fleming and tetracycline paved the way for better health for millions around the world. Before penicillin became a viable medical treatment in the early 1940s, no true cure for gonorrhea, strep throat, or pneumonia existed. Patients with infected wounds often had to have a wounded limb removed, or face death from infection. Now, most of these infections can be cured easily with a short course of antimicrobials.

The term antibiotic was first used in 1942 by Selman Waksman and his collaborators in journal articles to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This definition excluded substances that kill bacteria, but are not produced by microorganisms (such as gastric juices and hydrogen peroxide). It also excluded synthetic antibacterial compounds such as the sulfonamides. Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 atomic mass units. With advances in medicinal chemistry, most of today's antibacterials chemically are semisynthetic modifications of various natural compounds.

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13.1B: Antibiotic Discovery

Observations of antibiosis between micro-organisms led to the discovery of natural antibacterials produced by microorganisms.

Learning Objectives

- Describe the concept of ‘antibiosis’ and the contributions of the different scientists who discovered it

Key Points

- Before the early 20th century, treatments for infections were based primarily on medicinal folklore.
- Louis Pasteur observed, “if we could intervene in the antagonism observed between some bacteria, it would offer perhaps the greatest hopes for therapeutics”.
- The term ‘antibiosis’, meaning “against life,” was introduced by the French bacteriologist Vuillemin as a descriptive name of the phenomenon exhibited by these early antibacterial drugs.

Key Terms

- **micro-organism**: A microorganism (from the Greek: μ, mikrós, “small” and ὀ, organismós, “organism”; also spelled micro-organism, micro organism or microörganism) or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **chemotherapy**: Any chemical treatment intended to be therapeutic with respect to a disease state.
- **infection**: An uncontrolled growth of harmful microorganisms in a host.

Before the early 20th century, treatments for infections were based primarily on medicinal folklore. Mixtures with antimicrobial properties that were used in treatments of infections were described over 2000 years ago. Many ancient cultures, including the ancient Egyptians and ancient Greeks, used specially selected mold and plant materials and extracts to treat infections. More recent observations made in the laboratory of antibiosis between micro- organisms led to the discovery of natural antibacterials produced by microorganisms.

Louis Pasteur observed, “if we could intervene in the antagonism observed between some bacteria, it would offer perhaps the greatest hopes for therapeutics”. The term ‘antibiosis’, meaning “against life,” was introduced by the French bacteriologist Vuillemin as a descriptive name of the phenomenon exhibited by these early antibacterial drugs. Antibiosis was first described in 1877 in bacteria when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of Bacillus anthracis. These drugs were later renamed antibiotics by Selman Waksman, an American microbiologist, in 1942.

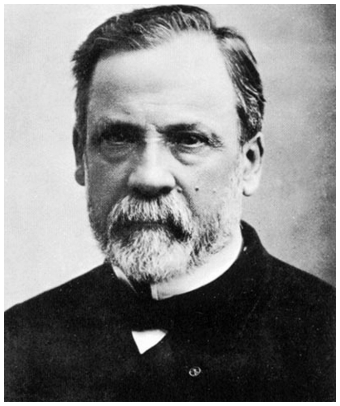

Figure: **Louis Pasteur**: Louis Pasteur was a French microbiologist and chemist best known for their experiments supporting the Germ theory of disease, and for his vaccinations, most notably the first vaccine against rabies.

John Tyndall first described antagonistic activities by fungi against bacteria in England in 1875. Synthetic antibiotic chemotherapy as a science and development of antibacterials began in Germany with Paul Ehrlich in the late 1880s. Ehrlich noted certain dyes would color human, animal, or bacterial cells, while others did not. He then proposed the idea that it might be possible to create chemicals that would act as a selective drug that would bind to and kill bacteria without harming the human host. After screening hundreds of dyes against various organisms, he discovered a medicinally useful drug, the synthetic antibacterial Salvarsan now called arsphenamine. In 1895, Vincenzo Tiberio, physician of the University of Naples discovered that a mold (Penicillium) in a water well has an antibacterial action. After this initial chemotherapeutic compound proved effective, others pursued similar lines

of inquiry, but it was not until in 1928 that Alexander Fleming observed antibiosis against bacteria by a fungus of the genus Penicillium. Fleming postulated the effect was mediated by an antibacterial compound named penicillin, and that its antibacterial properties could be exploited for chemotherapy. He initially characterized some of its biological properties, but he did not pursue its further development.

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13.1C: Antibiotics and Selective Toxicity

Antibiotics are able to selectively target specific types of bacteria without harming the infected host.

Learning Objectives

- Describe selective toxicity

Key Points

- Their mechanism of action, chemical structure, or spectrum of activity are ways in which antibiotics are classified.
- Broad spectrum antibiotics affect a wide range of bacteria, while narrow spectrum antibiotics are able to target specific types.
- Antibiotics must go through a screening process, where they are isolated, cultured, and then tested for production of diffusible products that inhibit the growth of specific test organisms.
- Due to potential adverse side effects, antibiotics must also be tested for their selective toxicities.

Key Terms

- **antibacterial**: A drug having the effect of killing or inhibiting bacteria.
- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.

Selective Toxicity in Antibiotics

Synthetic antibiotic chemotherapy as a science and development of antibacterials began in Germany with Paul Ehrlich in the late 1880s. Ehrlich noted that certain dyes would color human, animal, or bacterial cells, while others did not. He then proposed the idea that it might be possible to create chemicals that would act as a selective drug that would bind to and kill bacteria without harming the human host. After screening hundreds of dyes against various organisms, he discovered a medicinally useful drug, the synthetic antibacterial Salvarsan now called arsphenamine.

Antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. More specifically, narrow spectrum antibiotics target specific types of bacteria, such as Gram-negative or Gram-positive bacteria, whereas broad spectrum antibiotics affect a wide range of bacteria. Following a 40-year hiatus in discovering new classes of antibacterial compounds, three new classes of antibacterial antibiotics have been brought into clinical use: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), and oxazolidinones (such as linezolid).



Figure: **Bacterial Cultures**: In antibacterial production, microorganisms must be isolated, cultured, and tested for growth inhibition of target organisms and for their selective toxicity.

Some antibacterials have been associated with a range of adverse effects. Side-effects range from mild to very serious depending on the antibiotics used, the microbial organisms targeted, and the individual patient. Safety profiles of newer drugs are often not as well established as for those that have a long history of use. Adverse effects range from fever and nausea to major allergic reactions, including photodermatitis and anaphylaxis. Common side-effects include diarrhea, resulting from disruption of the

species composition in the intestinal flora, resulting, for example, in overgrowth of pathogenic bacteria, such as *Clostridium difficile*. Antibacterials can also affect the vaginal flora, and may lead to overgrowth of yeast species of the genus *Candida* in the vulvo-vaginal area. Additional side-effects can result from interaction with other drugs, such as elevated risk of tendon damage from administration of a quinolone antibiotic with a systemic corticosteroid.

Antibacterial Production

Despite the wide variety of known antibiotics, less than 1% of antimicrobial agents have medical or commercial value. For example, whereas penicillin has a high therapeutic index as it does not generally affect human cells, this is not so for many antibiotics. Other antibiotics simply lack advantage over those already in use, or have no other practical applications. Useful antibiotics are often discovered using a screening process. To conduct such a screen, isolates of many different microorganisms are cultured and then tested for production of diffusible products that inhibit the growth of test organisms. Most antibiotics identified in such a screen are already known and must therefore be disregarded. The remainder must be tested for their selective toxicities and therapeutic activities, and the best candidates can be examined and possibly modified. A more modern version of this approach is a rational design program. This involves screening directed towards finding new natural products that inhibit a specific target, such as an enzyme only found in the target pathogen, rather than tests to show general inhibition of a culture.

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13.1D: Spectrum of Antimicrobial Activity

An antibiotic's spectrum can be broad or narrow.

Learning Objectives

- Compare narrow and broad spectrum antibiotics

Key Points

- Broad spectrum antibiotics act against a larger group of bacteria.
- Narrow spectrum antibiotis target specific bacteria such as Gram positive or Gram negative.
- Three new classes of antibacterial antibiotics have been brought into clinical use: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), and oxazolidinones (such as linezolid).

Key Terms

- **Gram stain**: A method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative).
- **narrow spectrum antibiotic**: A type of antibiotic that targets specific types of Gram positive or Gram negative bacteria.
- **broad spectrum antibiotic**: A type of antibiotic that can affect a wide range of bacteria.

The range of bacteria that an antibiotic affects can be divided into narrow spectrum and broad spectrum. Narrow spectrum antibiotics act against a limited group of bacteria, either gram positive or gram negative, for example sodium fusidate only acts against staphylococcal bacteria. Broad spectrum—antibiotics act against gram positive and gram negative bacteria, for example amoxicillin.

Gram staining (or Gram's method; is a method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative). It is based on the chemical and physical properties of their cell walls. Primarily, it detects peptidoglycan, which is present in a thick layer in Gram positive bacteria. A Gram positive results in a purple/blue color while a Gram negative results in a pink/red color. The Gram stain is almost always the first step in the identification of a bacterial organism, and is the default stain performed by laboratories over a sample when no specific culture is referred. While Gram staining is a valuable diagnostic tool in both clinical and research settings, not all bacteria can be definitively classified by this technique, thus forming Gram-variable and Gram-indeterminate groups as well.

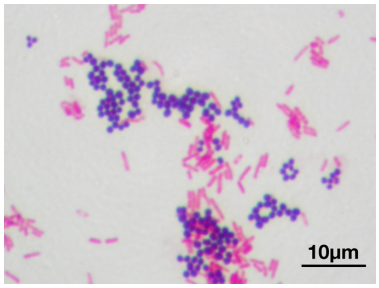

Figure: **Gram Stain**: This is a microscopic image of a Gram stain of mixed Gram-positive cocci (*Staphylococcus aureus*, purple) and Gram-negative bacilli (*Escherichia coli*, red).

A broad spectrum antibiotic acts against both Gram-positive and Gram-negative bacteria, in contrast to a narrow spectrum antibiotic, which is effective against specific families of bacteria. An example of a commonly used broad-spectrum antibiotic is ampicillin. Broad spectrum antibiotics are properly used in the following medical situations: empirically (i.e., based on the experience of the practitioner), prior to the formal identification of the causative bacteria and when there is a wide range of possible illnesses and a potentially serious illness would result if treatment is delayed. This occurs, for example, in meningitis, where the patient can become fatally ill within hours if broad-spectrum antibiotics are not initiated. Broad spectrum antibiotics are also used for drug resistant bacteria that do not respond to other, more narrow spectrum antibiotics and in the case of superinfections, where there are multiple types of bacteria causing illness, thus warranting either a broad-spectrum antibiotic or combination antibiotic therapy.

Following a 40-year hiatus in discovering new classes of antibacterial compounds, three new classes of antibacterial antibiotics have been brought into clinical use: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), and oxazolidinones (such as linezolid).

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13.1E: Antibiotic Classifications

Learning Objectives

Compare the two classes of antibiotics: bactericidal and bacteriostatic antibiotic

Antibiotics can be divided into two classes based on their mechanism of action. Bactericidal antibiotics kill bacteria; bacteriostatic antibiotics inhibit their growth or reproduction.

One way that bactericidal antibodies kill bacteria is by inhibiting cell wall synthesis. Examples include the Beta-lactam antibiotics (penicillin derivatives (penams)), cephalosporins (cephems), monobactams, and carbapenems) and vancomycin. Other ways that bactericidal antibiotics kill bacteria include inhibiting bacterial enzymes or protein translation. Other batericidal agents include daptomycin, fluoroquinolones, metronidazole, nitrofurantoin, co-trimoxazole and telithromycin. Aminoglycosidic antibiotics are usually considered bactericidal, although they may be bacteriostatic with some organisms. The MBC (minimum bactericidal concentration) is the minimum concentration of drug which can kill 99.99% of the population.

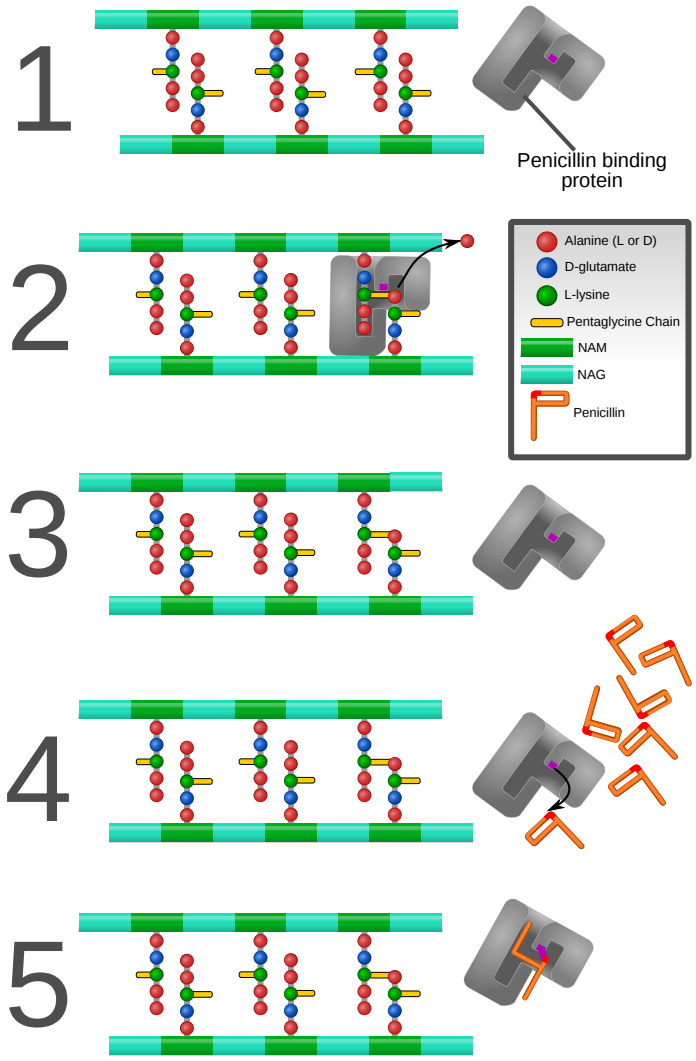

Figure: **Mechanism of penicillin inhibition**: Penicillin and most other β-lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.

Bacteriostatic antibiotics limit the growth of bacteria by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism. This group includes: tetracyclines, sulfonamides, spectinomycin, trimethoprim, chloramphenicol, macrolides and lincosamides. They must work together with the immune system to remove the microorganisms from the body. However, there is not always a precise distinction between them and bactericidal antibiotics. High concentrations of

some bacteriostatic agents are also bactericidal. The MIC (minimum inhibitory concentration) is the minimum concentration of drug which can inhibit the growth of the microorganism.

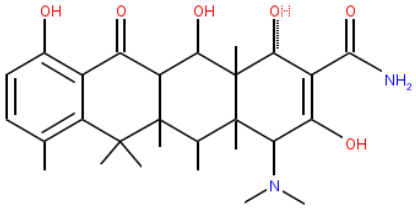

Figure: ***Structure of tetracycline****: Tetracycline antibiotics are protein synthesis inhibitors, inhibiting the binding of aminoacyl-tRNA to the mRNA-ribosome complex. They do so mainly by binding to the 30S ribosomal subunit in the mRNA translation complex.*

Further categorization is based on their target specificity. "Narrow-spectrum" antibacterial antibiotics target specific types of bacteria, such as Gram-negative or Gram-positive bacteria, whereas broad-spectrum antibiotics affect a wide range of bacteria, usually both gram positive and gram negative cells. Following a 40-year hiatus in discovering new classes of antibacterial compounds, three new classes of antibacterial antibiotics have been brought into clinical use: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), and oxazolidinones (such as linezolid).

Key Points

- Bactericidal antibodies inhibit cell wall synthesis.
- Bacteriostatic antibiotics limit the growth of bacteria by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism.
- Bacteriostatic antibiotics must work together with the immune system to remove the microorganisms from the body.

Key Terms

- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.

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SECTION OVERVIEW

13.2: Functions of Antimicrobial Drugs

Topic hierarchy

13.2A: Inhibiting Cell Wall Synthesis

13.2B: Injuring the Plasma Membrane

13.2C: Inhibiting Nucleic Acid Synthesis

13.2D: Inhibiting Protein Synthesis

13.2E: Inhibiting Essential Metabolite Synthesis

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13.2A: Inhibiting Cell Wall Synthesis

β-Lactam (beta-lactam) and glycopeptide antibiotics work by inhibiting or interfering with cell wall synthesis of the target bacteria.

Learning Objectives

- Describe the two types of antimicrobial drugs that inhibit cell wall synthesis: beta-lactam and glycopeptide antibiotics

Key Points

- The peptidoglycan layer is important for cell wall structural integrity, being the outermost and primary component of the wall.
- β-Lactam antibiotics are a broad class of antibiotics that includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.
- β-Lactam antibiotics are bacteriocidal and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls.
- Glycopeptide antibiotics include vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, and decaplanin.
- Glycopeptide antibiotics inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis.

Key Terms

- **beta-lactam antibiotic**: A broad class of antibiotics that inhibit cell wall synthesis, consisting of all antibiotic agents that contains a β-lactam nucleus in their molecular structures. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.
- **Glycopeptide antibiotic**: Glycopeptide antibiotics are composed of glycosylated cyclic or polycyclic nonribosomal peptides. Significant glycopeptide antibiotics include vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, and decaplanin. This class of drugs inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis.
- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.

Two types of antimicrobial drugs work by inhibiting or interfering with cell wall synthesis of the target bacteria. Antibiotics commonly target bacterial cell wall formation (of which peptidoglycan is an important component) because animal cells do not have cell walls. The peptidoglycan layer is important for cell wall structural integrity, being the outermost and primary component of the wall.

The first class of antimicrobial drugs that interfere with cell wall synthesis are the β-Lactam antibiotics (beta-lactam antibiotics), consisting of all antibiotic agents that contains a β-lactam nucleus in their molecular structures. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems. β-Lactam antibiotics are bacteriocidal and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The final step in the synthesis of the peptidoglycan is facilitated by penicillin-binding proteins (PBPs). PBPs vary in their affinity for binding penicillin or other β-lactam antibiotics.

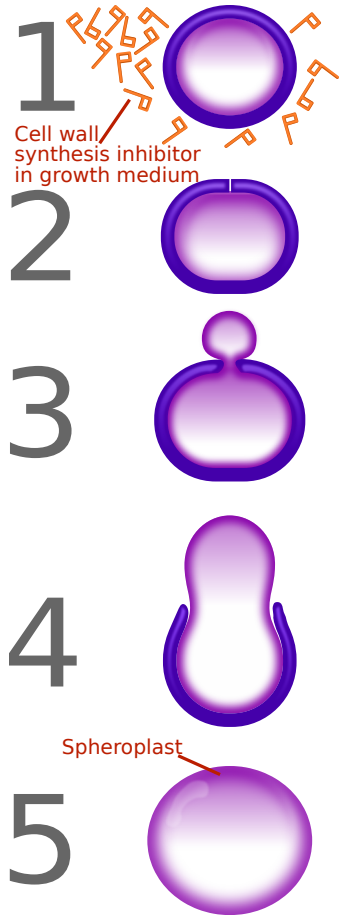

Figure: **Penicillin spheroplast generation**: Diagram depicting the failure of bacterial cell division in the presence of a cell wall synthesis inhibitor (e.g. penicillin, vancomycin).1- Penicillin (or other cell wall synthesis inhibitor) is added to the growth medium with a dividing bacterium.2- The cell begins to grow, but is unable to synthesize new cell wall to accommodate the expanding cell.3- As cellular growth continues, cytoplasm covered by plasma membrane begins to squeeze out through the gap(s) in the cell wall.4- Cell wall integrity is further violated. The cell continues to increase in size, but is unable to "pinch off" the extra cytoplasmic material into two daughter cells because the formation of a division furrow depends on the ability to synthesize new cell wall.5- The cell wall is shed entirely, forming a spheroplast, which is extremely vulnerable relative to the original cell. The loss of the cell wall also causes the cell to lose control over its shape, so even if the original bacterium were rod-shaped, the sphereoplast is generally spherical. Finally, the fact that the cell has now doubled much of its genetic and metabolic material further disrupts homeostasis, which usually leads to the cell's death.

Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid.

The second class of antimicrobial drugs that interfere with cell wall synthesis are the glycopeptide antibiotics, which are composed of glycosylated cyclic or polycyclic nonribosomal peptides. Significant glycopeptide antibiotics include vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, and decaplanin. This class of drugs inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis. They bind to the amino acids within the cell wall preventing the addition of new units to the peptidoglycan.

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13.2B: Injuring the Plasma Membrane

Several types of antimicrobial drugs function by disrupting or injuring the plasma membrane.

Learning Objectives

- Discuss the function of the plasma membrane and how antimicrobial drugs target it

Key Points

- The plasma membrane or cell membrane is a biological membrane that separates the interior of all cells from the outside environment.
- Plasma membranes are involved in a variety of cellular processes such as cell adhesion, ion conductivity, and cell signaling. They serve as the attachment surface for several extracellular structures, including the cell wall, glycocalyx, and intracellular cytoskeleton.
- Disrupting the plasma membrane causes rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death.

Key Terms

- **plasma membrane**: The semipermeable membrane that surrounds the cytoplasm of a cell.
- **cell wall**: A thick, fairly rigid layer formed around individual cells of bacteria, Archaea, fungi, plants, and algae, the cell wall is external to the cell membrane and helps the cell maintain its shape and avoid damage.
- **plasma cell**: a form of lymphocyte that produces antibodies when reacted with a specific antigen; a plasmacyte

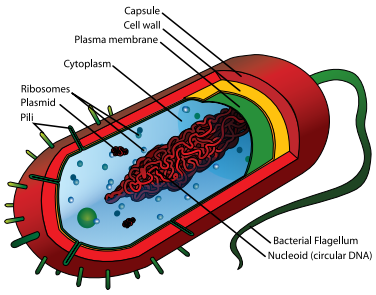

Figure: **Prokaryotic Cell**: Diagram of a typical gram-negative bacterium, with the thin cell wall sandwiched between the red outer membrane and the thin green plasma membrane.

The plasma membrane or cell membrane is a biological membrane that separates the interior of all cells from the outside environment. The plasma membrane is selectively permeable to ions and organic molecules. It controls the movement of substances in and out of cells. The membrane basically protects the cell from outside forces. It consists of the lipid bilayer with embedded proteins. Plasma membranes are involved in a variety of cellular processes such as cell adhesion, ion conductivity, and cell signaling. It serves as the attachment surface for several extracellular structures, including the cell wall, glycocalyx, and intracellular cytoskeleton. Fungi, bacteria, and plants also have the cell wall which provides a mechanical support for the cell and precludes the passage of larger molecules. The plasma membrane also plays a role in anchoring the cytoskeleton to provide shape to the cell and in attaching to the extracellular matrix and other cells to help group cells together to form tissues.

There are several types of antimicrobial drugs that function by disrupting or injuring the plasma membrane. One example is daptomycin, a lipopeptide which has a distinct mechanism of action, disrupting multiple aspects of bacterial cell membrane function. It appears to bind to the membrane causes rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Another example is polymyxins antibiotics which have a general structure consisting of a cyclic peptide with a long hydrophobic tail. They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids.

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13.2C: Inhibiting Nucleic Acid Synthesis

Antimicrobial drugs inhibit nucleic acid synthesis through differences in prokaryotic and eukaryotic enzymes.

Learning Objectives

- State the steps where inhibitors of nucleic acid synthesis can exert their function

Key Points

- Some antimicrobial drugs interfere with the initiation, elongation or termination of RNA transcription.
- Some antimicrobial drugs interfere with various aspects of DNA replication.
- The antimicrobial actions of these drugs are a result of differences in the prokaryotic and eukaryotic enzymes involved in nucleic acid synthesis.

Key Terms

- **transcription**: The synthesis of RNA under the direction of DNA.
- **replication**: Process by which an object, person, place or idea may be copied mimicked or reproduced.

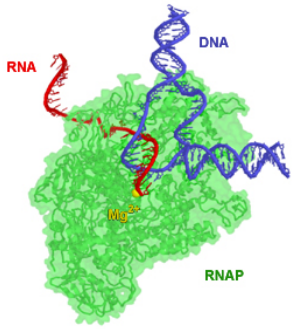

Figure: **Diagram of Transcription**: RNA Polymerase, an enzyme that produces RNA, from T. aquaticus pictured during elongation. Portions of the enzyme were made transparent so as to make the path of RNA and DNA more clear. The magnesium ion (yellow) is located at the enzyme active site.

Antimicrobial drugs can target nucleic acid (either RNA or DNA) synthesis. The antimicrobial actions of these agents are a result of differences in prokaryotic and eukaryotic enzymes involved in nucleic acid synthesis.

Prokaryotic transcription is the process in which messenger RNA transcripts of genetic material are produced for later translation into proteins. The transcription process includes the following steps: initiation, elongation and termination. Antimicrobial drugs have been developed to target each of these steps. For example, the antimicrobial rifampin binds to DNA-dependent RNA polymerase, thereby inhibiting the initiation of RNA transcription.

Other antimicrobial drugs interfere with DNA replication, the biological process that occurs in all living organisms and copies their DNA and is the basis for biological inheritance. The process starts when one double-stranded DNA molecule produces two identical copies of the molecule. In a cell, DNA replication begins at specific locations in the genome, called “origins. ” Uncoiling of DNA at the origin, and synthesis of new strands, forms a replication fork. In addition to DNA polymerase, the enzyme that synthesizes the new DNA by adding nucleotides matched to the template strand, a number of other proteins are associated with the fork and assist in the initiation and continuation of DNA synthesis. DNA replication, like all biological polymerization processes, proceeds in three enzymatically catalyzed and coordinated steps: initiation, elongation and termination. Any of the steps in the process of DNA replication can be targeted by antimicrobial drugs. For instance, quinolones inhibit DNA synthesis by interfering with the coiling of DNA strands.

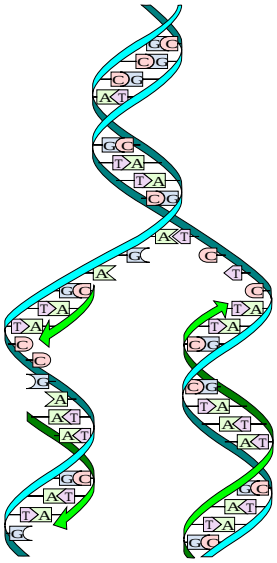

Figure: **DNA Replication**: The double helix is unwound and each strand acts as a template for the next strand. Bases are matched to synthesize the new partner strands.

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13.2D: Inhibiting Protein Synthesis

Protein synthesis inhibitors are substances that disrupt the processes that lead directly to the generation of new proteins in cells.

Learning Objectives

- Paraphrase the general mechanism of action of protein synthesis inhibitors

Key Points

- Protein synthesis inhibitors usually act at the ribosome level, taking advantage of the major differences between prokaryotic and eukaryotic ribosome structures.
- Protein synthesis inhibitors work at different stages of prokaryotic mRNA translation into proteins like initiation, elongation (including aminoacyl tRNA entry, proofreading, peptidyl transfer, and ribosomal translocation), and termination.
- By targeting different stages of the mRNA translation, antimicrobial drugs can be changed if resistance develops.

Key Terms

- **translation**: A process occurring in the ribosome, in which a strand of messenger RNA (mRNA) guides assembly of a sequence of amino acids to make a protein.

A protein synthesis inhibitor is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins. It usually refers to substances, such as antimicrobial drugs, that act at the ribosome level. The substances take advantage of the major differences between prokaryotic and eukaryotic ribosome structures which differ in their size, sequence, structure, and the ratio of protein to RNA. The differences in structure allow some antibiotics to kill bacteria by inhibiting their ribosomes, while leaving human ribosomes unaffected.

Translation in prokaryotes involves the assembly of the components of the translation system which are: the two ribosomal subunits (the large 50S & small 30S subunits), the mRNA to be translated, the first aminoacyl tRNA, GTP (as a source of energy), and three initiation factors that help the assembly of the initiation complex. The ribosome has three sites: the A site, the P site, and the E site (not shown in). The A site is the point of entry for the aminoacyl tRNA. The P site is where the peptidyl tRNA is formed in the ribosome. The E site which is the exit site of the now uncharged tRNA after it gives its amino acid to the growing peptide chain.

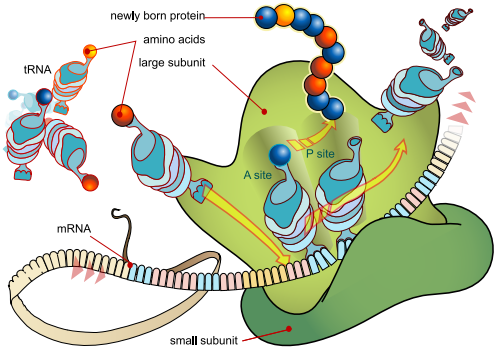

Figure: **Simplified diagram of protein synthesis**: Diagram showing how the translation of the mRNA and the synthesis of proteins is made by ribosomes.

In general, protein synthesis inhibitors work at different stages of prokaryotic mRNA translation into proteins like initiation, elongation (including aminoacyl tRNA entry, proofreading, peptidyl transfer, and ribosomal translocation), and termination. The following is a list of common antibacterial drugs and the stages which they target.

- Linezolid acts at the initiation stage, probably by preventing the formation of the initiation complex, although the mechanism is not fully understood.
- Tetracyclines and Tigecycline (a glycylcycline related to tetracyclines) block the A site on the ribosome, preventing the binding of aminoacyl tRNAs.
- Aminoglycosides, among other potential mechanisms of action, interfere with the proofreading process, causing an increased rate of error in synthesis with premature termination.

- Chloramphenicol blocks the peptidyl transfer step of elongation on the 50S ribosomal subunit in both bacteria and mitochondria.
- Macrolides, clindamycin, and aminoglycosides have evidence of inhibition of ribosomal translocation.
- Streptogramins also cause premature release of the peptide chain.

By targeting different stages of the mRNA translation, antimicrobial drugs can be changed if resistance develops to one or many of the drugs.

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13.2E: Inhibiting Essential Metabolite Synthesis

An antimetabolite is a chemical that inhibits the use of a metabolite, a chemical that is part of normal metabolism.

Learning Objectives

- Distinguish between the three main types of antimetabolite antibiotics (antifolates, pyrimidine and purine analogues)

Key Points

- The presence of antimetabolites can have toxic effects on cells, such as halting cell growth or cell division.
- Antimetabolites are also used as antibiotics.
- The three main types of antimetabolite antibiotics are antifolates, pyrimidine analogues and purine analogues.

Key Terms

- **antimetabolite**: Any substance that competes with or inhibits the normal metabolic process, often by acting as an analogue of an essential metabolite

An antimetabolite is a chemical that inhibits the use of a metabolite, a chemical that is part of normal metabolism. Such substances are often similar in structure to the metabolite that they interfere with, such as antifolates that interfere with the use of folic acid. The presence of antimetabolites can have toxic effects on cells, such as halting cell growth or cell division.

Antimetabolites are also used as antibiotics. There are three main types of antimetabolite antibiotics. The first, antifolates impair the function of folic acid leading to disruption in the production of DNA and RNA. For example, methotrexate is a folic acid analogue, and owing to structural similarity with folic acid, methotrexate binds and inhibits the enzyme dihydrofolate reductase, and thus prevents the formation of tetrahydrofolate. Because tetrahydrofolate is essential for purine and pyrimidine synthesis, its deficiency can lead to inhibited production of DNA, RNA and proteins.

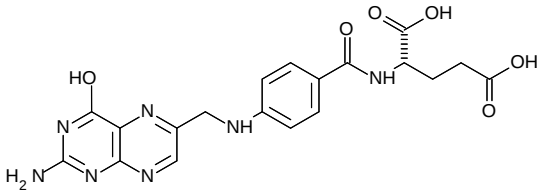

Figure: **Folic Acid Structure**: This is the chemical structure of folic acid.

The second type of antimetabolite antibiotics consist of pyrimidine analogues which mimic the structure of metabolic pyrimidines. Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives and the pyrimidine analogues disrupt their formation and consequently disrupt DNA and RNA synthesis.

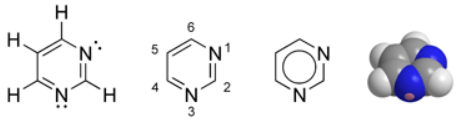

Figure: **Pyrimidine Structure**: This is the chemical structure of pyrimidine.

The purine analogues are the third type of antimetabolite antibiotics and they mimic the structure of metabolic purines. Two of the four bases in nucleic acids, adenine and guanine, are purines. Purine analogues disrupt nucleic acid production. For example, azathioprine is the main immunosuppressive cytotoxic substance that is widely used in transplants to control rejection reactions by inhibiting DNA synthesis in lymphocytes.

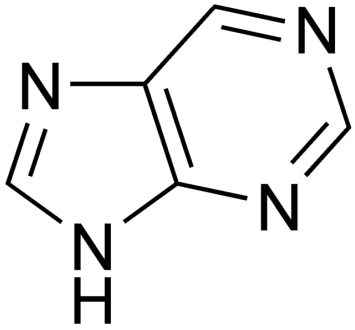

Figure: **Purine Structure**: This is the chemical structure of purine.

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SECTION OVERVIEW

13.3: Commonly Used Antimicrobial Drugs

Topic hierarchy

13.3A: Synthetic Antimicrobial Drugs

13.3B: Naturally Occurring Antimicrobial Drugs: Antibiotics

13.3C: Beta-Lactam Antibiotics: Penicillins and Cephalosporins

13.3D: Antibiotics from Prokaryotes

13.3E: Antimycobacterial Antibiotics

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13.3A: Synthetic Antimicrobial Drugs

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans.

Learning Objectives

- Recall the synthetic antimicrobial drugs that are sulfonamide and sulphonamide based

Key Points

- The discovery of antimicrobials like penicillin and tetracycline paved the way for better health for millions around the world.
- With the development of antimicrobials, microorganisms have adapted and become resistant to previous antimicrobial agents.
- Synthetic agents include: sulphonamides, cotrimoxazole, quinolones, anti-virals, anti-fungals, anti-cancer drugs, anti-malarials, anti-tuberculosis drugs, anti-leprotics, and anti-protozoals.

Key Terms

- **antimicrobial**: An agent that destroys microbes, inhibits their growth, or prevents or counteracts their pathogenic action.
- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **bacteria**: A type, species, or strain of bacterium.

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). Disinfectants are antimicrobial substances used on non-living objects or outside the body.

The history of antimicrobials begins with the observations of Pasteur and Joubert, who discovered that one type of bacteria could prevent the growth of another. They did not know at that time that the reason one bacterium failed to grow was that the other bacterium was producing an antibiotic. Technically, antibiotics are only those substances that are produced by one microorganism that kill, or prevent the growth, of another microorganism. Of course, in today's common usage, the term antibiotic is used to refer to almost any drug that attempts to rid your body of a bacterial infection. Antimicrobials include not just antibiotics, but synthetically formed compounds as well.

The discovery of antimicrobials like penicillin and tetracycline paved the way for better health for millions around the world. Before penicillin became a viable medical treatment in the early 1940s, no true cure for gonorrhea, strep throat, or pneumonia existed. Patients with infected wounds often had to have a wounded limb removed, or face death from infection. Now, most of these infections can be cured easily with a short course of antimicrobials.

However, with the development of antimicrobials, microorganisms have adapted and become resistant to previous antimicrobial agents. The old antimicrobial technology was based either on poisons or heavy metals, which may not have killed the microbe completely, allowing the microbe to survive, change, and become resistant to the poisons and/or heavy metals.

Antimicrobial nanotechnology is a recent addition to the fight against disease-causing organisms, replacing heavy metals and toxins, and may some day be used as a viable alternative.

Infections that are acquired during a hospital visit are called "hospital acquired infections" or nosocomial infections. Similarly, when the infectious disease is picked up in the non-hospital setting, it is considered "community acquired".

Synthetic agents include: sulphonamides, cotrimoxazole, quinolones, anti-virals, anti-fungals, anti-cancer drugs, anti-malarials, anti-tuberculosis drugs, anti-leprotics, and anti-protozoals.

Sulfonamide or sulphonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sometimes called sulfa drugs or sulpha drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides.

Sulfa allergies are common, and medications containing sulfonamides are prescribed carefully. It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group and do not cause the same hypersensitivity reactions seen in the sulfonamides.

In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis. As such, the microorganism will be “starved” of folate and die.

The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide, and torsemide), sulfonylureas (including glipizide, glyburide, among others), and some COX-2 inhibitors (e.g., celecoxib), and acetazolamide.

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13.3B: Naturally Occurring Antimicrobial Drugs: Antibiotics

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans.

Learning Objectives

- Discuss the mechanism of action for protein synthesis inhibitors used as antimicrobial drugs, and recognize various naturally occuring antimicrobial drugs

Key Points

- There are mainly two classes of antimicrobial drugs: those obtained from natural sources (i.e. beta-lactam antibiotic (such as penicillins, cephalosporins) or protein synthesis inhibitors (such as aminoglycosides, macrolides, tetracyclines, chloramphenicol, polypeptides); and synthetic agents.
- A β-lactam (beta-lactam) ring is a four-membered lactam. A lactam is a cyclic amide. It is named as such because the nitrogen atom is attached to the β-carbon relative to the carbonyl.
- A protein synthesis inhibitor is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins.

Key Terms

- **β-lactam**: A β-lactam (beta-lactam) ring is a four-membered lactam. A lactam is a cyclic amide. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The simplest β-lactam possible is 2-azetidinone.
- **antimicrobial**: An agent that destroys microbes, inhibits their growth, or prevents or counteracts their pathogenic action.
- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.

An antimicrobial is a substance that kills or inhibits the growth of microorganisms bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). Disinfectants are antimicrobial substances used on non-living objects or outside the body.

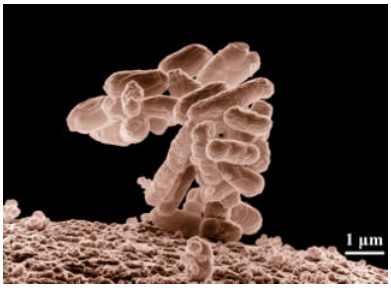

Figure: **A cluster of Escherichia coli Bacteria magnified 10,000 times.**: A cluster of Escherichia coli Bacteria magnified 10,000 times.

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There are mainly two classes of antimicrobial drugs: those obtained from natural sources (i.e. beta-lactam) antibiotic (such as penicillins, cephalosporins) or protein synthesis inhibitors (such as aminoglycosides, macrolides, tetracyclines, chloramphenicol,

polypeptides); and synthetic agents.

A β-lactam (beta-lactam) ring is a four-membered lactam. A lactam is a cyclic amide. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The simplest β-lactam possible is 2-azetidinone.

A protein synthesis inhibitor is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins. While a broad interpretation of this definition could be used to describe nearly any antibiotic, in practice, it usually refers to substances that act at the ribosome level (either the ribosome itself or the translation factor), taking advantage of the major differences between prokaryotic and eukaryotic ribosome structures. Toxins such as ricin also function via protein synthesis inhibition. Ricin acts at the eukaryotic 60S.

In general, protein synthesis inhibitors work at different stages of prokaryotic mRNA translation into proteins, like initiation, elongation (including aminoacyl tRNA entry, proofreading, peptidyl transfer, and ribosomal translocation), and termination. Rifamycin inhibits prokaryotic DNA transcription into mRNA by inhibiting DNA-dependent RNA polymerase by binding its beta-subunit. Linezolid acts at the initiation stage probably by preventing the formation of the initiation complex, although the mechanism is not fully understood.

Tetracyclines and Tigecycline (a glycylcycline related to tetracyclines) block the A site on the ribosome, preventing the binding of aminoacyl tRNAs. Aminoglycosides, among other potential mechanisms of action, interfere with the proofreading process, causing increased rate of error in synthesis with premature termination. Chloramphenicol blocks the peptidyl transfer step of elongation on the 50S ribosomal subunit in both bacteria and mitochondria. Macrolides (as well as inhibiting ribosomal translocation and other potential mechanisms) bind to the 50s ribosomal subunits, inhibiting peptidyl transfer. Quinupristin/dalfopristin act synergistically, with dalfopristin, enhancing the binding of quinupristin as well as inhibiting peptidyl transfer. Quinupristin binds to a nearby site on the 50S ribosomal subunit and prevents elongation of the polypeptide. It also causes incomplete chains to be released. Macrolides, clindamycin, and aminoglycosides (with all these three having other potential mechanisms of action as well) have evidence of inhibition of ribosomal translocation. Fusidic acid prevents the turnover of elongation factor G (EF-G) from the ribosome. Macrolides and clindamycin (both also having other potential mechanisms) cause premature dissociation of the peptidyl-tRNA from the ribosome. Puromycin has a structure similar to that of the tyrosinyl aminoacyl-tRNA. Therefore, it binds to the ribosomal A site and participates in peptide bond formation, producing peptidyl-puromycin. However, it does not engage in translocation and quickly dissociates from the ribosome, causing a premature termination of polypeptide synthesis.

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13.3C: Beta-Lactam Antibiotics: Penicillins and Cephalosporins

The β-lactam ring is part of the core structure of several antibiotic families.

Learning Objectives

- Recognize the classes of beta-lactams and their mechanisms of action

Key Points

- The principal antibiotic families of which the β-lactam ring is part of the core structure are the penicillins, cephalosporins, carbapenems, and monobactams, which are also called β-lactam antibiotics.
- A β-lactam (beta-lactam) ring is a four-membered lactam (cyclic amide). -Lactams are classified according to their core ring structures.
- The cephalosporins are a class of β-lactam antibiotics originally derived from the fungus Acremonium, which was previously known as “Cephalosporium”.

Key Terms

- **cephalosporins**: The cephalosporins are a class of β-lactam antibiotics originally derived from the fungus Acremonium, which was previously known as “Cephalosporium”.
- **antibiotic**: Any substance that can destroy or inhibit the growth of bacteria and similar microorganisms.
- **β-lactam**: A β-lactam (beta-lactam) ring is a four-membered lactam. A lactam is a cyclic amide. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The simplest β-lactam possible is 2-azetidinone.
- **β-lactam**: Any of a class of cyclic amides, that are the nitrogen analogs of lactones, formed by heating amino acids; the tautomeric enol forms are known as lactims.

A β-lactam (beta-lactam) ring, is a four-membered lactam. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The simplest β-lactam possible is 2-azetidinone.

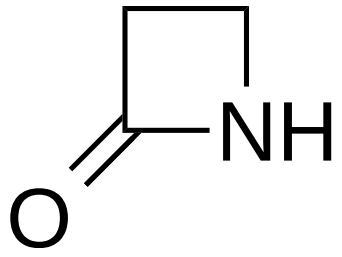

Figure: **β-Lactam**: β-Lactam ring is a four-membered lactam.

The β-lactam ring is part of the core structure of several antibiotic families, the principal ones being the penicillins, cephalosporins, carbapenems, and monobactams, which are, therefore, also called β-lactam antibiotics. Nearly all of these antibiotics work by inhibiting bacterial cell wall biosynthesis. This has a lethal effect on bacteria. Bacteria do, however, contain within their populations, in smaller quantities, bacteria that are resistant against β-lactam antibiotics. They do this by expressing the β-lactamase gene. When bacterial populations have these resistant subgroups, treatment with β-lactam can result in the resistant strain becoming more prevalent and so, more virulent.

β-Lactams are classified according to their core ring structures:

- β-Lactams fused to saturated five-membered rings;
- β-Lactams containing thiazolidine rings are named *penams*;
- β-Lactams containing pyrrolidine rings are named *carbapenams*;
- β-Lactams fused to oxazolidine rings are named *oxapenams* or *clavams*;
- β-Lactams fused to unsaturated five-membered rings;
- β-Lactams containing 2,3-dihydrothiazole rings are named *penems*;
- β-Lactams containing 2,3-dihydro-1H-pyrrole rings are named *carbapenems*;
- β-Lactams fused to unsaturated, six-membered rings;
- β-Lactams containing 3,6-dihydro-2H-1,3-thiazine rings are named *cephems*;
- β-Lactams containing 1,2,3,4-tetrahydropyridine rings are named *carbacephems*;

- β-Lactams containing 3,6-dihydro-2H-1,3-oxazine rings are named *oxacephems*; and
- β-Lactams not fused to any other ring are named *monobactams*.

Penicillin (sometimes abbreviated PCN or pen) is a group of antibiotics derived from *Penicillium fungi.* They include penicillin G, procaine penicillin, benzathine penicillin, and penicillin V. Penicillin antibiotics are historically significant because they are the first drugs that were effective against many previously serious diseases, such as syphilis, and infections caused by staphylococci and streptococci. Penicillins are still widely used today, though many types of bacteria are now resistant. All penicillins are β-lactam antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

The cephalosporins (sg. /ˌsɛfələʊspɔɾɨn/) are a class of β-lactam antibiotics originally derived from the fungus Acremonium, which was previously known as “Cephalosporium”. Together with cephamycins, they constitute a subgroup of β-lactam antibiotics called *cephems*. Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. First-generation cephalosporins are active predominantly against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms).

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13.3D: Antibiotics from Prokaryotes

Most of the currently available antibiotics are produced by prokaryotes mainly by bacteria from the genus *Streptomyces*.

Learning Objectives

- Explain the role of Streptomyces and other prokaryotes in antibiotic production

Key Points

- Gramicidin is one of the first antibiotics to be manufactured commercially. It is a heterogeneous mixture of six antibiotic compounds, all of which are obtained from the soil bacterial species Bacillus brevis.
- Streptomyces is the largest antibiotic-producing genus, producing antibacterial, antifungal, and antiparasitic drugs, and also a wide range of other bioactive compounds, such as immunosuppressants. They produce over two-thirds of the clinically useful antibiotics of natural origin.
- Members of the Streptomyces genus are the source for numerous antibacterial pharmaceutical agents; among the most important of these are: Chloramphenicol (from S. venezuelae), Lincomycin (from S. lincolnensis), Neomycin (from S. fradiae), Tetracycline (from S. rimosus and S. aureofaciens).
- Some Pseudomonas spp. might produce compounds antagonistic to other soil microbes, such as phenazine-type antibiotics or hydrogen cyanide.

Key Terms

- **antibiotic**: Any substance that can destroy or inhibit the growth of bacteria and similar microorganisms.
- **beta-lactamase**: An enzyme produced by certain bacteria, responsible for their resistance to beta-lactam antibiotics such as penicillin.

Even though penicillin drugs, antibiotics produced by molds, were the first antibiotics successfully used to treat many serious infections, most of the naturally produced antibiotics are synthesized by bacteria. In 1939 the French microbiologist René Dubos isolated the substance tyrothricin and later showed that it was composed of two substances, gramicidin (20%) and tyrocidine (80%). These were the first antibiotics to be manufactured commercially. Gramicidin is a heterogeneous mixture of six antibiotic compounds, all of which are obtained from the soil bacterial species *Bacillus brevis* and called collectively gramicidin D.

Streptomyces is the largest antibiotic-producing genus, producing antibacterial, antifungal, and antiparasitic drugs, and also a wide range of other bioactive compounds, such as immunosuppressants. They produce over two-thirds of the clinically useful antibiotics of natural origin. The now uncommonly-used streptomycin takes its name directly from *Streptomyces*. Aminoglycosides, class of antibiotics, that are derived from bacteria of the *Streptomyces* genus are named with the suffix -mycin, whereas those that are derived from *Micromonospora* are named with the suffix -micin. However, this nomenclature system is not specific for aminoglycosides.



Figure: **Supernatant of a Streptomyces davawensis culture**: The picture shows the typical red color of the antibiotic Roseoflavin secreted by the Streptomyces cells in the culture.

Streptomycetes are characterised by a complex secondary metabolism. Almost all of the bioactive compounds produced by *Streptomyces* are initiated during the time coinciding with the aerial hyphal formation from the substrate mycelium.

Streptomycetes produce numerous antifungal compounds of medicinal importance, including nystatin (from *S. noursei*), amphotericin B (from *S. nodosus*), and natamycin (from *S. natalensis*).

Members of the *Streptomyces* genus are the source for numerous antibacterial pharmaceutical agents; among the most important of these are: Chloramphenicol (from *S. venezuelae*), Daptomycin (from *S. roseosporus*), Fosfomycin (from *S. fradiae*), Lincomycin (from *S. lincolnensis*), Neomycin (from *S. fradiae*), Puromycin (from *S. alboniger*), Streptomycin (from *S. griseus*), Tetracycline (from *S. rimosus* and *S. aureofaciens*).

Clavulanic acid (from *S. clavuligerus*) is a drug used in combination with some antibiotics (like amoxicillin) to block and/or weaken some bacterial-resistance mechanisms by irreversible beta-lactamase inhibition.

Other bacterial species produce antibiotics as well. Such an example are some *Pseudomonas* species which produce antimicrobial compounds. *P. aurantiaca* produces di-2,4-diacetylfluoroglucylmethane, a compound antibiotically active against Gram-positive organisms. Other *Pseudomonas* spp. might produce compounds antagonistic to other soil microbes, such as phenazine-type antibiotics or hydrogen cyanide.

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13.3E: Antimycobacterial Antibiotics

Antimycobacterial antibiotics target microbes classified as mycobacterium.

Learning Objectives

- Compare and contrast the drugs used for treatment of Mycobacterium tuberculosis and Mycobacterium leprae

Key Points

- The standard “short” course treatment for TB is isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, then isoniazid and rifampicin alone for another four months.
- The standard treatment for leprosy is a multidrug therapy that includes dapsone, clofazimine and rifampicin.
- Mycobacterium are defined by their ability to grow in a mold-like fashion on the surface of liquids when cultured.

Key Terms

- **tuberculosis**: Tuberculosis, MTB, or TB (short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis.
- **infectious disease**: Infectious diseases, also known as transmissible diseases or communicable diseases comprise of clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism. In certain cases, infectious diseases may be asymptomatic for much or even all of their course in a given host. In the latter case, the disease may only be defined as a “disease” (which by definition means an illness) in hosts who secondarily become ill after contact with an asymptomatic carrier. An infection is not synonymous with an infectious disease, as some infections do not cause illness in a host.
- **leprosy**: Leprosy, also known as Hansen’s disease (HD), is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis.
- **isoniazid**: a medication used in the prevention and treatment of tuberculosis, having the chemical formula C6H7N3O

Antimycobacterial antibiotics are a class of antimicrobial drugs that target mycobacterium. Mycobacterium is a genus of Actinobacteria that includes pathogens known to cause serious and infectious disease. The types of pathogens considered to be mycobacterium include Mycobacterium tuberculosis (tuberculosis) and Mycobacterium leprae (leprosy). Mycobacterium grow in a mold-like manner on the surface of liquids when cultured. Antiomycobacterial antibiotics specifically target these types of microbes.

A type of antimycobacterial antibiotic includes the class of drugs used for tuberculosis (TB) treatment. The standard “short” course treatment for TB is isoniazid, rifampicin (also known as rifampin in the United States), pyrazinamide and ethambutol for two months, then isoniazid and rifampicin alone for another four months. The patient is considered cured at six months (although there is still a relapse rate of 2 to 3%). For latent tuberculosis, the standard treatment is six to nine months of isoniazid alone.

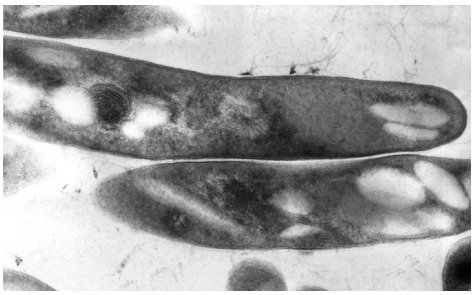

Figure: **Mycobacterium**: Mycobacterium are a class of bacteria defined by their ability to grow in a mold-like manner. Here, a TEM of Mycobacterium tuberculosis, the causative agent of tuberculosis. Antimycobacterial antibiotics target mycobacterium.

If the organism is known to be fully sensitive, then it is treated with isoniazid, rifampicin and pyrazinamide for two months, followed by isoniazid and rifampicin for four months. Ethambutol need not be used. Most regimens have an initial high-intensity phase, followed by a continuation phase (also called a consolidation phase or eradication phase) – the high-intensity phase is given first, then the continuation phase.

There are six classes of second-line drugs (SLDs) used for the treatment of TB. A drug may be classed as second-line instead of first-line for one of three possible reasons: it may be less effective than the first-line drugs (e.g., p-aminosalicylic acid); or, it may

have toxic side-effects (e.g., cycloserine); or it may be unavailable in many developing countries (e.g., fluoroquinolones): aminoglycosides: e.g., amikacin (AMK), kanamycin (KM); polypeptides: e.g., capreomycin, viomycin, enviomycin; Fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF); thioamides: e.g. ethionamide, prothionamide.

For treatment of leprosy, caused by Mycobacterium leprae, the traditional antimycobacterial drugs include promin (the first treatment introduced to fight leprosy) and dapsone (which eventually become obsolete as Mycobacterium leprae quickly evolved resistance). Modern drugs which were developed in response to the resistance was clofazimine and rifampicin. The use of multidrug therapies including dapsone, clofazimine and rifampicin were advantageous due to the low risk of antibiotic resistance. However, the use of these multidrug treatments was costly and only adopted in endemic countries when the World Health Assembly passed a resolution to eliminate leprosy in 1991.

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SECTION OVERVIEW

13.4: Interactions Between Drug and Host

Topic hierarchy

13.4A: Organ Toxicity

13.4B: Allergic Responses to Drugs

13.4C: Suppression and Alteration of Microbiota by Antimicrobials

13.4D: Effects of Drug Combinations

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13.4A: Organ Toxicity

The accumulation of antimicrobial drugs and their metabolic byproducts in organs can be toxic, leading to organ damage.

Learning Objectives

- Outline the two major types of organ toxicity and their effects, recognizing additional types of toxicity

Key Points

- Antimicrobial drugs can have unintended side effects, including being toxic to organs.
- The liver and kidney are particularly susceptible to organ toxicity as they are the sites of toxin filtration and toxin metabolic breakdown.
- Almost any organ or tissue in the human body can be affected by antimicrobial toxicity.
- The toxic effects of antimicrobial drugs, while potentially harmful are very rare.

Key Terms

- **antimicrobrial drugs**: A drug administered to a patient, with the purpose of killing or slowing the growth of a microorganism, including protozoans, fungi and bacteria.
- **antibiotics**: A chemical that slows the growth of, or kills a bacteria.

The use of antimicrobial drugs can have many unintended side-effects. The use, particularly when repeated, of many drugs can lead to an accumulation of a drug, or harmful byproducts from the metabolism of a drug, in tissues or organs. This accumulation of toxic chemicals can lead to organ damage, and in extreme cases, even organ failure and death. Two severe types of organ toxicity associated with antimicrobial drugs are nephrotoxicity and hepatotoxicity, toxicity of the kidneys and liver respectively.

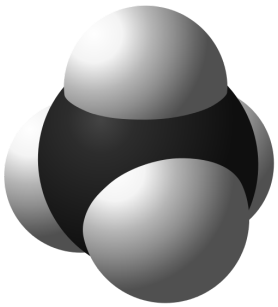

Figure: **Methane**: This space-filling model of methane shows the approximately spherical nature of this molecule.

The liver and kidneys are common organs affected by chemical toxicity. The kidneys are responsible for the filtration of the blood, so it is not surprising that deleterious agents in the blood may accumulate there. The liver is an important site for the breakdown of most metabolites in the body, and is referred to as the “metabolic clearing house” of the body. As drugs are quite often broken down in the liver, they can accumulate there and cause damage, or the byproducts of a drug’s metabolism can be toxic. In addition to direct damage to the liver by an antimicrobial drug, antimicrobial drugs can lead to the formation of dangerous toxins through the breakdown of microbes or due to interaction with other tissues in the body. These secondary toxins from drug metabolism then accumulate in the liver, potentially causing damage. Drug damage to the liver or kidneys can be particularly catastrophic as these organs are needed for the proper “cleaning” of the body. If they are compromised, this leads to further accumulation of potentially toxic metabolites further damaging organs in the body.



Figure: **Sun Poisoning**: This rash seen on a forearm is a typical reaction observed when an antibiotic causes phototoxicity.

Some of the toxic effects can be more benign, as is the case with ototoxicity, or damage to the ear. Use of some antibiotics, such as gentamicin, can cause a lose of hearing, or tinnitus (“ringing in the ears”). Ototoxicity is usually temporary with antibiotics, but permanent hearing damage, while rare, has been reported. Some antibiotics such as Tetracycline can cause phototoxicity, also known as sun poisoning; the result of which is that very short exposures to direct sunlight can cause severe skin irritation, with the appearance being quite similar to a rash or sunburn. The Tetracycline in a patient’s skin becomes toxic when exposed to sunlight, which causes an allergic reaction and leads to rash on the affected area. Broad-spectrum antibiotics in the family of fluoroquinolones can cause neurotoxicity by directly damaging neuronal receptors. This can lead to any number of psychological effects from mild cognitive dysfunction (brain fog) to more severe effects, such as hallucinations and suicidal thoughts.

While a few specific examples have been outlined here, toxic effects are not limited to the organs mentioned. In fact, almost any tissue or organ can be affected by antimicrobial drugs. However, it should be noted that the side-effects due to broad-spectrum antibiotics are actually quite rare, with organ damage being even more rare.The potential side-effects of antibiotics or other antimicrobial drugs are offset by the benefits of combating the microbial infection.

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13.4B: Allergic Responses to Drugs

Antimicrobrial drugs can cause immune responses which can be fatal.

Learning Objectives

- Explain the physiology of an immune response responsible for an allergic reaction to drugs

Key Points

- Antimicrobial drugs, can like almost any other substance, act as an allergen.
- Using a drug may not induce an allergic response the first time it is taken, however, subsequent use of the antimicrobial drugs may lead to allergic reactions.
- The most common antimicrobial drug allergy is penicillin. 1-5% of people who have taken it have suspected penicillin allergies.

Key Terms

- **allergen**: A substance, known as an antigen, which stimulates an immune response from a sensitive individual.
- **anaphylaxis**: A rapid and severe allergic reaction which can lead to death
- **Beta-lactam antibiotics**: A broad class of antibiotics of which penicillin is a member.

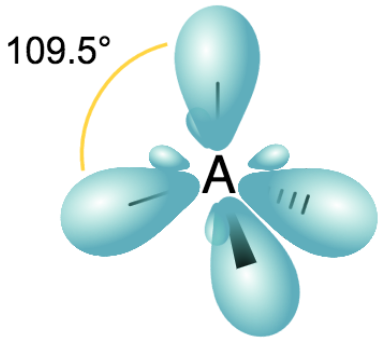

Figure: **sp3 hybridization**: In the process of sp^3 hybridization in methane, the single 2s and three 2p orbitals of carbon mix into four sp^3 hybrid orbitals, which are chemically and geometrically identical. Bond angles are 109.5°.

Virtually any substance, when exposed internally or externally to the body, can act as an allergen and illicit an immune system response, such is the case with antimicrobial drugs. While the drug acts as an allergen, the drug itself is not causing direct damage to the individual, but rather it is the response of an individual's immune system which is deleterious. An allergic reaction is the body's response to clear a foreign substance. Once the body recognizes a substance as foreign (in this case an antimicrobial drug), it starts producing antibodies, specifically immunoglobulin E (IgE) against the drug. The IgE binds directly to the drug and sets off a cascade of events, including the activation of receptors on immune system cells. This results in the production of histamines. The worst allergic reactions can be very severe and result in anaphylaxis. Anaphylaxis is an extremely severe allergic reaction caused when histamines are overproduced leading to severe contraction of bronchial muscles. In the most extreme cases, the airways close, which can lead to death. Other less severe symptoms of an allergic reaction can include, hives, angioedema (tissue swelling under the skin, often on the face), tight throat, coughing, wheezing, or watery eyes.

The exposure to a drug may not elicit an allergic reaction during the first exposure, but after the first exposure, the body creates antibodies and memory lymphocyte cells against the drug, therefore later exposures to the drug will illicit an immune response. There are many factors that can determine if an individual is sensitive to an antimicrobial drug, as with other allergens. Some factors include genetics and past exposures to other allergens, typically a person who has allergies to other things, such as various foods, is more prone to have or develop drug allergies. The most reported drug allergy is to Beta-lactam antibiotics, of which penicillin is the most well-known type, affecting 1-5% of people who take penicillin. While the most severe cases can result in anaphylaxis, most reactions are not severe. Additionally the allergic reaction may not even be due to the penicillin, as dyes and other chemicals added to antimicrobial drugs may in fact cause the allergic response instead. Taken together, recent studies show that perhaps only 1/5 people who suspect they have an allergy to penicillin do indeed have such an allergy.

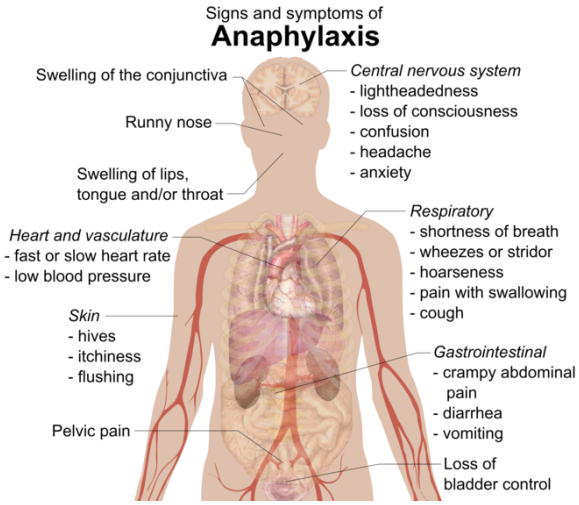

Figure: **Anaphylaxis**: A representation of the signs and symptoms of anaphylaxis that result from an allergic reaction. Signs include CNS symptoms such as confusion or lightheadedness, respiratory symptoms such as shortness of breath, gastrointestinal issues such as pain or vomiting, skin issues such as hives or itchiness, vascular symptoms such as change in heart rate or low blood pressure, and swelling of the mouth or eyes.

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13.4C: Suppression and Alteration of Microbiota by Antimicrobials

Our bodies depend upon, and host, a vast number of complex microbial flora that can be affected negatively by antimicrobial treatments.

Learning Objectives

- Describe the role and function of the microbiota

Key Points

- The intestinal system has many different species of microbes and huge numbers of individual microbes; we rely on these microbes for proper metabolism of food.
- The use of antimicrobial agents to slow down or kill pathogenic microbes can often kill beneficial bacteria, causing deleterious health effects.
- Our body hosts some microbes that inhibit the growth of pathogenic microbes; using antimicrobial agents can alter the flora allowing pathogenic microbes to overgrow and cause diseases.

Key Terms

- **Candidal vulvovaginitis**: Candidal vulvovaginitis or vaginal thrush, or yeast infection, is an infection of the vagina's mucous membranes by Candida albicans.
- **microbiota**: The microbial flora harbored by normal, healthy individuals.
- **pathogenic bacteria**: Bacteria which infect and cause deleterious health effects.

The human body hosts thousands of different species of microbial organisms, known as the microbial flora or microbiota. Microbiota serve many functions in our body; most notable is the gut flora, crucial for the proper digestion of food, carbohydrate fermentation, and nutrient absorption. The gut flora in the human intestinal system has hundreds of species of microbes and over 100 trillion individual microbes; in comparison, the human body has around 10 trillion cells. Most of these microbes are bacterial and fungal. This is especially a problem when broad-spectrum antimicrobial agents are used, as antimicrobial treatments while helping to clear up pathogenic microbes from the body will often kill symbiotic bacteria. In addition, some microbial infections are due to translocation, the movement of advantageous bacteria to parts of the body where they might be harmful. An example is gut flora getting into the body's blood stream. The treatment of translocated or pathogenic bacteria may necessitate the use of antibiotics that will kill symbiotic bacteria. Antimicrobial agents which can kill beneficial gut flora can reduce the numbers of individual microbes or reduce the species of beneficial bacteria. In the case of the gut flora, this may impair the ability of a patient to properly metabolize food. If advantageous bacteria do not repopulate the intestine, this can lead to serious malnutrition problems.

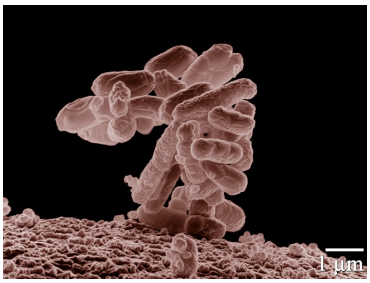

Figure: **Gut bacteria**: This is an electron micrograph, at 10,000X magnification. The oblong structures are Escherichia coli (E. coli), a symbiotic bacteria found in the human intestinal system.

In addition to serving a necessary function as gut flora due in metabolism of food, some microbiota in our bodies serve the function of keeping pathogenic microbes from inhabiting or dominating other flora at locations in our body. This is exemplified by Candida albicans, a yeast which is often found on humans. C. albicans is normally harmless, but when women take some antibiotics this can kill beneficial bacteria, specifically lactobacilli, in the vulvo-vaginal area. Without lactobacilli, C. albicans growth is not suppressed and can thus overgrow. This causes candidal vulvovaginitis, or yeast infections, a potentially painful infection of the vaginal mucous membranes by overgrown C. albicans. Yeast infections can be caused by antibiotics, as well as using aggressive topical cleaning agents such as detergents which again kill off beneficial lactobacilli allowing C. albicans to overgrow.

Fortunately there are antimicrobial agents that specifically target pathogenic bacterial species, which opposed to broad-spectrum treatments can reduce harmful effects on beneficial microbes. Sometimes the use of broad-spectrum antimicrobial agents is unavoidable; in these situations, consuming foods such as yogurt which contains beneficial bacteria can replenish the body's symbiotic microbes. In extreme cases microbes can be transplanted from a healthy individual to someone with whose symbiotic microbes have been compromised.

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13.4D: Effects of Drug Combinations

Antimicrobial drugs can interact with other drugs in deleterious ways or can be used in combination to combat microbial infections.

Learning Objectives

- Give examples of interactions that can render an antimicrobial ineffective

Key Points

- The interaction between one antimicrobial agent and another is very complex, along with the way they target microbes and the organism.
- While it is not certain that a drug may interact with antibiotics, it is considered wise to err on the side that there are potentially unknown and harmful interactions from mixing drugs.
- The use of more than one antimicrobial agent is an effective and widely used practice to reduce the chance that microbes will resist a treatment.

Key Terms

- **contraindication**: In medicine, a contraindication is a condition or factor that serves as a reason to withhold a certain medical treatment.
- **tuberculosis**: An infectious disease of humans and animals caused by a species of mycobacterium mainly infecting the lungs where it causes tubercles characterized by the expectoration of mucus and sputum, fever, weight loss, and chest pain, and transmitted through inhalation or ingestion of bacteria.
- **combination therapy**: Combination therapy is the use of more than one medication or other therapy. Most often, these terms refer to the simultaneous administration of two or more medications to treat a single disease.

Pharmacodynamics is the field that attempts to understand the unintended effects of the use of two or more drugs. Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body. It also looks at the mechanisms of drug action and the relationship between drug concentration and effect. These changes are extraordinarily difficult to classify given the wide variety of modes of action that exist and the fact that many drugs can cause their effect through a number of different mechanisms. This wide diversity also means that, in all but the most obvious cases, it is important to investigate and understand these mechanisms. The well-founded suspicion exists that there are more unknown interactions than known ones.

Two well described interactions between antimicrobial drugs and other drugs are between antibiotics and alcohol and antibiotics and the birth control pill. Interactions between alcohol and certain antibacterials may occur, cause side-effects, and decrease effectiveness of antibacterial therapy. Potential risks of side-effects and effectiveness depend on the type of antibacterial administered. Despite the lack of a categorical contraindication, the belief that alcohol and antibacterials should never be mixed is widespread. Some antibacterials may inhibit the breakdown of alcohol, which may result in alcohol-induced vomiting, nausea, and shortness of breath. Other effects of alcohol on antibacterial activity include altered activity of the liver enzymes that break down the antibacterial compound. In addition, serum levels bacteriostatic antibacterials may be reduced by alcohol consumption, resulting in reduced efficacy and diminished pharmacotherapeutic effect.

Another well studied interaction is between antibiotics and the contraceptive pill. The majority of studies indicate that antibiotics do not interfere with contraceptive pills. In cases where antibacterials have been suggested to affect the efficiency of birth control pills may be due to an increase in the activities of hepatic liver enzymes causing increased breakdown of the pill's active ingredients. Effects on the intestinal flora, which might result in reduced absorption of estrogens in the colon, have also been suggested, but such suggestions have been inconclusive and controversial. Clinicians have recommended that extra contraceptive measures be applied during therapies using antibacterials that are suspected to interact with oral contraceptives.

Additionally, when dealing with a microbial infection, sometimes the use of two or more antibiotics can effectively combat the infection while each drug individually has little or no effect. This method is called combination therapy and is used when the nature of a microbial infection is unknown, as typified by the combination of the antibiotics ampicillin and sulbactam. The use of two antibiotics with different modes of microbial inhibition increases the chance that the treatment will combat the microbial infection. Further, tuberculosis has been treated with combination therapy for over fifty years. This is due to the phenomenon of resistance, whereby a micro-organism gains the ability to resist an antimicrobial drug, while initially the drug effectively slowed the growth of

or even killed the target micro-organism. Treating tuberculosis, or other pathogenic microbes with more than one antibiotic reduces the chance that the microbe will adapt and survive the treatment, especially if the two drugs have different methods of reducing the microbe's normal functions.



Figure: **Tuberculosis**: This x-ray of a tuberculosis patient shows the lung on the left side completely infected and the right lung partially infected (the dark areas), with tuberculosis.

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SECTION OVERVIEW

13.5: Measuring Drug Susceptibility

Topic hierarchy

13.5A: Minimal Inhibitory Concentration (MIC)

13.5B: Kirby-Bauer Disk Susceptibility Test

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13.5A: Minimal Inhibitory Concentration (MIC)

Minimum Inhibitory Concentration is the lowest drug concentration that prevents visible microorganism growth after overnight incubation.

Learning Objectives

- Analyze data to interpret minimal inhibitory concentration values

Key Points

- Minimum inhibitory concentration (MIC) can be determined by culturing microorganisms in liquid media or on plates of solid growth medium.
- A lower MIC value indicates that less drug is required for inhibiting growth of the organism; therefore, drugs with lower MIC scores are more effective antimicrobial agents.
- By identifying appropriate drugs and their effective concentrations, MIC scores aid in improving outcomes for patients and preventing evolution of drug-resistant microbial strains.

Key Terms

- **culture**: The process of growing a bacterial or other biological entity in an artificial medium.
- **minimum inhibitory concentration**: This is the lowest concentration of an antimicrobial drug that prevents visible growth of a microorganism after overnight incubation with media.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.

Definition and Measurement

In microbiology, minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial (like an antifungal, antibiotic or bacteriostatic) drug that will inhibit the visible growth of a microorganism after overnight incubation. MICs can be determined on plates of solid growth medium (called agar, shown in the “Kirby-Bauer Disk Susceptibility Test” atom) or broth dilution methods (in liquid growth media, shown in) after a pure culture is isolated. For example, to identify the MIC via broth dilution, identical doses of bacteria are cultured in wells of liquid media containing progressively lower concentrations of the drug. The minimum inhibitory concentration of the antibiotic is between the concentrations of the last well in which no bacteria grew and the next lower dose, which allowed bacterial growth. There are also several commercial methods available to experimentally measure MIC values.

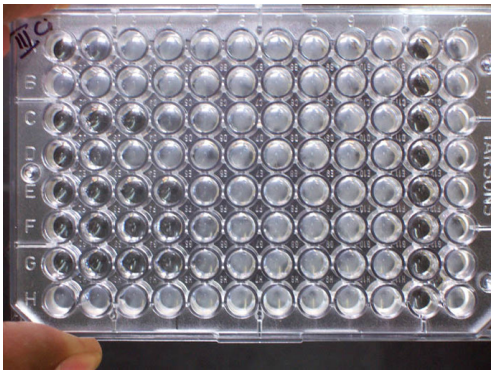

Figure: **Microbroth Dilution Method**: To identify the lowest concentration required for a given antibiotic to inhibit bacterial growth, an identical amount of bacteria is introduced into wells of liquid media containing progressively lower concentrations of the drug. (Here, the dilution series of the drug is set up from left to right: for example, well E1 might contain 100 units of drug; E2, 50 units; E3, 25 units; E4, 12.5 units; etc.). Because bacterial growth made the media in well E5 cloudy and the media in well E4 is indistinguishable from clear media, this indicates that the minimum inhibitory concentration is between the drug concentrations in wells E4 and E5. (Image courtesy of Microrao, Dept. of Microbiology, JJMMC, Davangere).

Significance and Applications

An MIC is generally regarded as the most basic laboratory measurement of the activity of an antimicrobial agent against an organism. Because a lower MIC value indicates that less of the drug is required in order to inhibit growth of the organism, drugs with lower MIC scores are more effective antimicrobial agents. Currently, there are a few web-based, freely accessible MIC databases. MIC scores are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents. Clinicians use MIC scores to choose which antibiotics to administer to patients with specific infections and to identify an effective dose of antibiotic. This is important because populations of bacteria exposed to an insufficient concentration of a particular drug or to a broad-spectrum antibiotic (one designed to inhibit many strains of bacteria) can evolve resistance to these drugs. Therefore, MIC scores aid in improving outcomes for patients and preventing evolution of drug-resistant microbial strains.

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13.5B: Kirby-Bauer Disk Susceptibility Test

Learning Objectives

- Review the procedure for the Kirby-Bauer antibiotic tes

Kirby-Bauer antibiotic testing (also called KB testing or disk diffusion antibiotic sensitivity testing) uses antibiotic-containing wafers or disks to test whether particular bacteria are susceptible to specific antibiotics. First, a pure culture of bacteria is isolated from the patient. Then, a known quantity of bacteria are grown overnight on agar (solid growth media) plates in the presence of a thin wafer that contains a known amount of a relevant antibiotic. If the bacteria are susceptible to the particular antibiotic from a wafer, an area of clear media where bacteria are not able to grow surrounds the wafer, which is known as the zone of inhibition. A larger zone of inhibition around an antibiotic-containing disk indicates that the bacteria are more sensitive to the antibiotic in the disk.

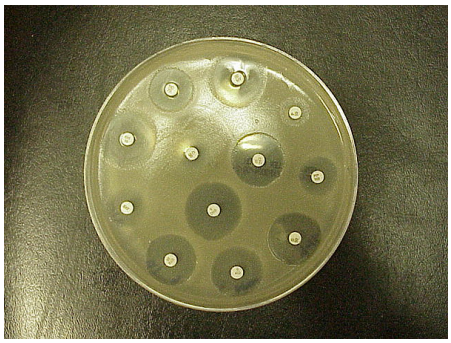

Figure: ***Kirby-Bauer test****: In Kirby–Bauer testing, discs containing antibiotics are placed on agar where bacteria are growing, and the antibiotics diffuse out into the agar. If an antibiotic stops the bacteria from growing, one can see circular areas around the wafers where bacteria have not grown.*

KB tests are performed under standardized conditions and standard-sized zones of inhibition have been established for each antibiotic. KB test results are usually reported as sensitive, intermediate, or resistant, based on the size of the zone of inhibition. If the observed zone of inhibition is greater than or equal to the size of the standard zone, the microorganism is considered to be sensitive to the antibiotic. Conversely, if the observed zone of inhibition is smaller than the standard size, the microorganism is considered to be resistant. The size of a zone of inhibition in a KB test is inversely related to the minimum inhibitory concentration (MIC), which is the amount of antibiotic required to prevent bacterial growth in an overnight culture. The MIC (in µg/ml) can be calculated from known standard-curve (linear regression) graphs based on the diameter of the observed inhibition zone diameter (in millimeters).

Clinicians can use KB test results to choose appropriate antibiotics to combat a particular infection in a patient. Administering antibiotics that specifically target the particular bacteria that are causing the infection can avoid using broad-spectrum antibiotics, which target many types of bacteria. Thus, clinical application of KB testing results can decrease the frequency with which antibiotic-resistant bacteria evolve.

Key Points

- KB tests are performed under standard conditions, so the minimum inhibitory concentration for a given antibiotic can be calculated by comparing the observed zone of inhibition ‘s size to known values.
- Clinicians use KB test results to choose antibiotics effective against the specific bacteria causing a patient’s infection. Using specifically-targeted antibiotics helps decrease the frequency of drug-resistant bacteria evolving.

Key Terms

- **Kirby-Bauer antibiotic testing**: This is a method to determine the sensitivity of microorganisms to specific antimicrobial drugs; greater drug efficacy yields larger microbe-free zones surrounding drug-containing disks after overnight growth on solid media.
- **zone of inhibition**: This is an area of media where bacteria are unable to grow, due to presence of a drug that impedes their growth.

- **minimum inhibitory concentration**: This is the lowest concentration of an antimicrobial drug that prevents visible growth of a microorganism after overnight incubation with media.

13.5B: Kirby-Bauer Disk Susceptibility Test is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

SECTION OVERVIEW

13.6: Drug Resistance

Topic hierarchy

13.6A: Mechanisms of Resistance

13.6B: Antibiotic Misuse

13.6C: Cost and Prevention of Resistance

13.6D: Biofilms, Persisters, and Antibiotic Tolerance

13.6E: Finding New Antimicrobial Drugs

13.6F: Antimicrobial Peptides

13.6G: Antisense Agents

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13.6A: Mechanisms of Resistance

Development of microbial resistance to antimicrobial agents requires alterations in the microbe's cell physiology and structure.

Learning Objectives

- Describe the mechanisms bacteria use to develop antimicrobial resistance and the factors that can lead to it

Key Points

- Antimicrobial resistance can be mediated by the environment or the microorganism itself.
- Environmentally-mediated antimicrobial resistance results from physical or chemical characteristics of the environment that can affect the antimicrobial agent or the microorganism.
- Microorganism-mediated antimicrobial resistance can be intrinsic or acquired.

Key Terms

- **intrinsic**: innate, inherent, inseparable from the thing itself, essential.

Development of microbial resistance to antimicrobial agents requires alterations in the microbe ‘s cell physiology and structure. Antimicrobial resistance is defined as the loss of susceptibility to an extent that the drug is no longer effective for clinical use against an organism. Resistance can be mediated by the environment or the microorganism itself.

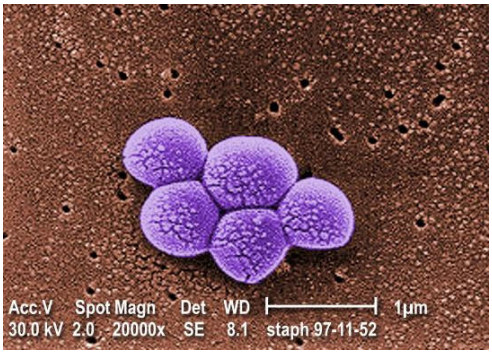

Figure: **Resistant bacterial strain**: Methicillin-resistant Staphylococcus aureus.

Environmentally-mediated antimicrobial resistance is affected by the environment's chemical and physical properties such as pH, anaerobic conditions, cation concentrations (calcium, magnesium), and thymine-thymidine content (available metabolites and nutrients).

Microorganism-mediated antimicrobial resistance is due to genetically-encoded traits of the microorganism and can be divided into intrinsic or acquired. Intrinsic resistance is considered to be a natural and inherited property with high predictability. Once the identity of the organism is known, the aspects of its anti-microbial resistance are also recognized. On the other hand, acquired resistance results from a change in the organism's genetic makeup. This trait is associated with only some strains of an organism's group but not the others. It is also an unpredictable trait and necessitates the development of laboratory methods to detect it. Microorganism-mediated antimicrobial resistance is acquired by gene change or exchange such as genetic mutations, acquisition of genes from other organisms via gene transfer mechanisms, or a combination of mutational and gene transfer events. Some common pathways bacteria use to effect antimicrobial resistance include: enzymatic degradation or modification of the antimicrobial agent, decreased uptake or accumulation of the antimicrobial agent, altered antimicrobial target, circumvention of consequences of antimicrobial actions, uncoupling of antimicrobial agent-target interaction, or any combination of these mechanisms.

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13.6B: Antibiotic Misuse

Learning Objectives

- Explain the effects of antibiotic misuse

With the introduction of antibiotics into medical practice, clinically-relevant bacteria have had to adopt resistance mechanisms as part of their survival strategy. Antibiotic resistance occurs when antibiotics no longer work against disease-causing bacteria. These infections are difficult to treat and can mean longer-lasting illnesses, more doctor visits or extended hospital stays, and the need for more expensive and toxic medications. Some resistant infections can even cause death. Developing new antibiotics and other treatments to keep pace with antibiotic-resistant strains of bacteria is necessary. However, using antibiotics wisely is equally important for preventing the spread of resistant strains.

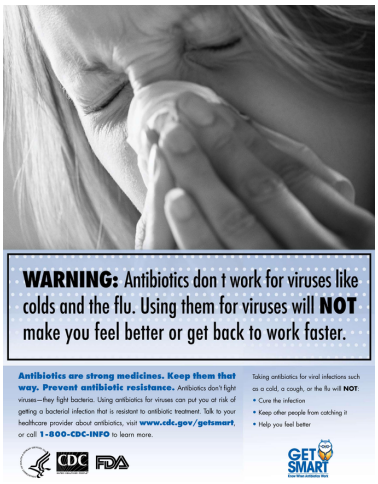

Figure: ***Figure 13.6B.1****: Antibiotic misuse. Antibiotics are not effective against viral infections. Misusing them leads to resistant bacterial strains.*

Antibiotic misuse has contributed largely to the emergence of new resistant strains. It is caused by taking an antibiotic too often for a condition it cannot treat such as viral infections and the common cold or in the wrong doses. It can also be manifested by not finishing a course of antibiotics as prescribed (stopping the antibiotic before the infection is fully cleared from the body). Overuse of antibiotics affects the bodsy's normal flora and disrupts the balance between beneficial bacteria that help digestion for example, and harmful bacteria. Excessive use of antibiotics in intensive farming units, particularly pig and poultry farms, is also seen as a growing threat. Scientists say antimicrobial resistance may be passing between animals and humans through food consumption, making the need to cut unnecessary use of antibiotics in farming even more urgent. Responsible antibiotic use in industry, and good practice for patients and physicians, are essential to keep resistant bacterial strains curable, and antibiotic treatment affordable to patients.

Key Points

- Antimicrobial resistance is a major public health concern.
- Antimicrobial resistance is brought about by antibiotic misuse, such as overuse, misuse, or interrupted treatment.
- Food industries, physicians, and patients play a role in minimizing the spread of resistance by adhering to good antibiotic practice.

Key Terms

- **course of antibiotics**: a period of continuous treatment with a drug.

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13.6C: Cost and Prevention of Resistance

Learning Objectives

- Examine the causes and effects of multidrug-resistant organisms on healthcare

Prevention and control of microbial-resistant organisms is one of the most complex management issues that health care professionals face. The clinical and financial burden to patients and health care providers is staggering. Patients who are infected with bacterial strains resistant to more than one type or class of drugs (multidrug-resistant organisms, MDRO) often have an increased risk of prolonged illness, extended hospital stay, and mortality.

The cost of care for these patients can be more than double compared to those without an MDRO infection. The alternative medication they are prescribed to overcome the infection is often substantially more costly. Multidrug resistance forces healthcare providers to use antibiotics that are more expensive or more toxic to the patient.



Figure: ***Antibiotics****: Antibiotic misuse is a major cause of the staggering healthcare costs for the treatment of resistant bacterial strains.*

When no antibiotic is effective, healthcare providers may be limited to providing supportive care rather than directly treating an infection. In a 2008 study of attributable medical costs for antibiotic resistant infections, it was estimated that infections in 188 patients from a single healthcare institution cost between $13.35 and $18.75 million dollars.

Research and development of new drugs effective against resistant bacterial strains also comes at a cost. To prevent antimicrobial resistance, the patient and the healthcare provider should discuss the appropriate medicine for the illness. Patients should follow prescription directions and should not share or take medicine that was prescribed for someone else; these virtues should be strictly practiced. Healthy lifestyle habits, including proper diet, exercise, and sleeping patterns, as well as good hygiene such as frequent hand washing, can help prevent illness. These practices, therefore, also help prevent the overuse or misuse of antibiotics and the emergence of problematic resistant strains.

Key Points

- Antimicrobial resistance to available drugs requires the development of new drugs to effectively treat resistant strains and reduce mortality from bacterial infections.
- Antimicrobial resistance can be prevented by practicing good hygiene, and being responsible with antibiotic use.
- Treating antibiotic-resistant bacterial strains is expensive for both the patient and the healthcare provider. The treatment requires extended hospital stay and costly medications.

Key Terms

- **multidrug resistance**: A condition enabling a disease-causing organism to resist distinct drugs or chemicals of a wide variety of structure and function targeted at eradicating the organism.

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13.6D: Biofilms, Persisters, and Antibiotic Tolerance

Biofilms and persisters are bacterial communities responsible for chronic diseases and antibiotic tolerance.

Learning Objectives

- Explain the role of biofilms and persisters in multidrug tolerance, distinguishing this from multidrug resistance

Key Points

- Biofilms are aggregates of microbial cells that form to avoid antimicrobial agents or attack by the immune system.
- Persisters are slow-growing, dormant microbial cells that can tolerate antibiotic treatment.
- Biofilms and persisters are responsible for chronic bacterial infections and recurrent disease.
- Antibiotic tolerance is different from antibiotic resistance but equally important as a public health burden for eradication of serious bacterial diseases.

Key Terms

- **gingivitis**: inflammation of the gums or gingivae
- **extracellular matrix**: All the connective tissues and fibers that are not part of a cell, but rather provide support.

Biofilms are bacteria that have formed a gated community. Biofilms are composed of an aggregate of bacterial cells and are essentially considered a multi-cellular organism. They are characterized by structural heterogeneity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances. They live on solid surfaces (e.g., catheters,) and the extracellular material they produce protects them from external threats, such as attacks by the body's immune cells. The property of biofilms constitute a penetration barrier for most antibiotics therefore preventing the drug from reaching the microbes. It is being widely recognized that bacterial biofilms are responsible for several chronic diseases that are difficult to treat, hence hard to eradicate (e.g., cystitis, endocarditis, urinary tract infections, gingivitis, dental plaque, and other yet to be identified conditions). They differ from free-floating or planktonic bacteria that cause acute infections and are managed by antimicrobial drugs.

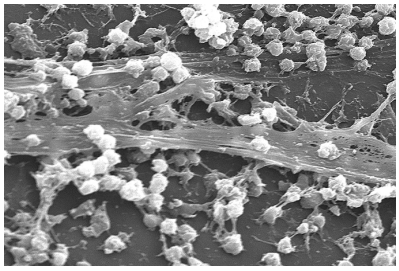

Figure: **Staphylococcus aureus biofilm**: Staphylococcus aureus forming a biofilm on a catheter.

Persisters are multidrug tolerant cells present in all bacterial populations. Bacterial populations that produce persister cells that neither grow nor die in the presence of microbicidal antibiotics are largely responsible for high levels of biofilm tolerance to antimicrobials. Persisters are not mutants, but rather phenotypic variants of the wild-type that upon inoculation produce a culture with similar levels of tolerance. Elimination of persisters remains an obstacle for the eradication of some tenacious and highly recurrent bacterial infections. Biofilms and persisters are the cause of multidrug tolerance. Multidrug tolerance differs from multidrug resistance in that it is not caused by mutant microbes but rather by microbial cells that exist in a transient, dormant state. These non-dividing cells often survive antibiotic exposure targeted to kill highly proliferating bacteria.

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13.6E: Finding New Antimicrobial Drugs

Antimicrobial resistance has created a public health crisis in the treatment of infectious diseases and necessitates the discovery of new drugs.

Learning Objectives

- Explain the reasons for low production of new antibiotics and discuss the proposed mechanisms to evade antimicrobial resistance

Key Points

- Finding new antimicrobial drugs requires researchers, pharmaceutical, and biotech companies to invest in new technology and discover new sources for antibiotic development.
- Proposed mechanisms to circumvent antimicrobial resistance range from exploring the list of resistance genes to antibody-based therapy and vaccines.
- Finding new candidates to target is essential but it needs to be accompanied by awareness on antibiotic misuse with the prospect to eliminate the root of the problem.

Key Terms

- **mimetic**: A substance with similar pharmacological effects to another substance.

Antimicrobial resistance: the problem

Antibiotics, more than any other medicines, have improved the life expectancy of mankind, however, multi-drug resistance has become common in pathogenic bacteria and multiple drugs are losing efficacy. Recent reports on the occurrence of panresistant gram-negative strains, i.e. strains resistant to every registered antibacterial drug, indicate that we are on the verge to lose the battle, taking us back to the pre-antibiotic era. There is world-wide consensus that the medical need for novel antiinfective drugs is enormous and that we are running out of time. Many achievements of modern medicine, not only treatment of infectious diseases, depend on the availability of efficacious antibiotics, still, the antibacterial development pipeline is slow and the number of new drugs reaching the market is alarmingly low. There are many reasons for this at all levels of the discovery and development process. Investments into antibiotic research and technologies is minimal; socioeconomic considerations together with regulatory hurdles have prompted pharmaceutical companies to exit the field and innovative biotech companies were confronted with problems beyond their control. Answers are needed as to where and how we can find new lead compounds with unprecedented activities?

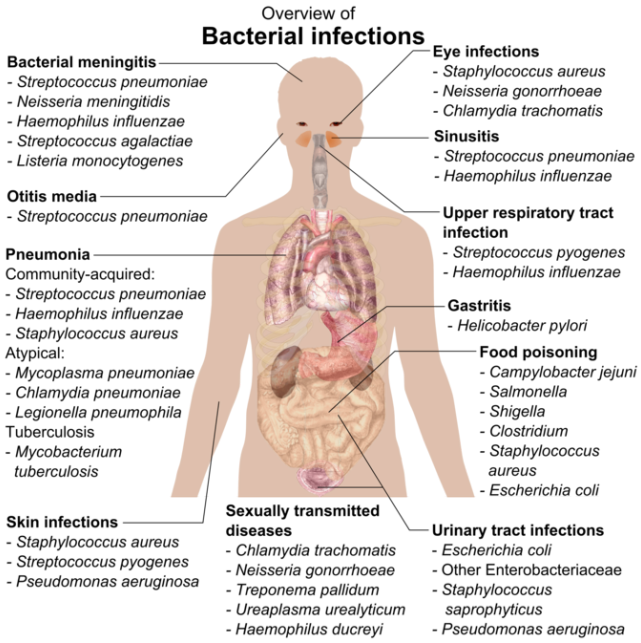

Figure: **Bacterial infections of the human body**: most bacterial species listed in this figure have developed resistance to available antibiotics necessitating new drug discovery.

Finding new antimicrobial drugs: the solution

Research on new antimicrobial compounds is geared towards innovative targets to circumvent resistance. Some of the proposed areas to investigate include: collecting and examining the list of antimicrobial resistance genes (e.g. exploring the resistome), targeting teichoic acid biosynthesis as a new method to compromise the bacterial wall integrity, producing ribosomal inhibitors to target protein synthesis, targeting outer-membrane transporters with protein epitope mimetics (e.g. mimetics of the cationic antimicrobial peptides that form part of the immune response to microbes), and developing antibody-based strategies and vaccines. The initiative to develop new antimicrobial agents is urgently needed but is a long process from invention, to development, to actual clinical application. It is also necessary to initiate a worldwide awareness on antibiotic misuse and overuse as a mean to address the root of the problem for antimicrobial resistance.

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13.6F: Antimicrobial Peptides

Antimicrobial peptides exhibit cytotoxic activity against all microbes.

Learning Objectives

- Discuss the structure, mechanism, and targets of antimicrobial peptides

Key Points

- Antimicrobial peptides (AMPs) are a unique and assorted group of molecules produced by living organisms of all types, considered to be part of the innate immunity of a host.
- These peptides demonstrate potent antimicrobial activity and are rapidly mobilized to neutralize a broad range of microbes, such as viruses, bacteria, protozoa, and fungi.
- The ability of these natural molecules to kill multidrug-resistant microorganisms has gained them considerable attention and clinical interest.

Key Terms

- **neutropenia**: A hematological disorder characterized by an abnormally low neutrophil count.
- **atopic dermatitis**: An atopic, hereditary, and non-contagious skin disease characterized by chronic inflammation of the skin.

A first line of defense against pathogenic insult is called the innate immune system, which is followed by acquired immune responses associated with the activation of T and B cells aimed against specific antigens. In contrast to the clonal, acquired adaptive immunity, endogenous peptide antibiotics or antimicrobial peptides provide a fast and energy-effective mechanism as front-line defense.

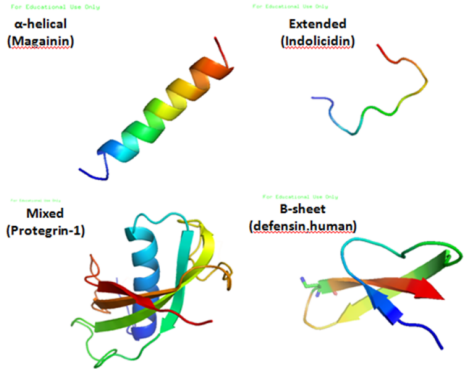

Figure: **Various AMPs**: These are various antimicrobial peptide structures.

Antimicrobial peptides (AMPs) are small molecular weight proteins with broad spectrum antimicrobial activity against bacteria, viruses, and fungi. They are classified on the basis of their structure and amino acid motifs. Peptides of the defensin, cathelicidin, and histatin classes are found in humans. These evolutionarily conserved peptides are usually positively charged and have both a hydrophobic and hydrophilic side that enables the molecule to be soluble in aqueous environments yet also enter lipid-rich membranes. Once in a target microbial membrane, the peptide kills target cells through diverse mechanisms. AMPs secrete lytic enzymes, nutrient-binding proteins or contain sites that target specific microbial macromolecules.

Cathelicidins and defensins are major groups of epidermal AMPs. Decreased levels of these peptides have been noted for patients with atopic dermatitis and Kostmann's syndrome, a congenital neutropenia. AMPs have proven effective against multidrug-resistant microbes. In addition to important antimicrobial properties, growing evidence indicates that AMPs alter the host immune response through receptor-dependent interactions. AMPs have been shown to be important in such diverse functions as angiogenesis, wound healing, cytokine release, chemotaxis, and regulation of the adaptive immune system. These peptides qualify as innovative drugs that might be used as antibiotics, anti-lipopolysaccharide drugs, or modifiers of inflammation reactions.

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13.6G: Antisense Agents

Learning Objectives

- Discuss the mechanism of antisense agents and the advantages and disadvantages of antisense therapy.

Antisense agents are synthetic, single-stranded short sequences of DNA bases designed to hybridize to specific sequences of messenger RNA (mRNA) forming a duplex. This DNA-RNA coupling attracts an endogenous nuclease, RNase H that destroys the bound RNA and frees the DNA antisense to rehybridize with another copy of mRNA. In this way, the effect is not only highly specific but prolonged because of the recycling of the antisense DNA sequence. When this agent binds to the pathogen DNA or messenger RNA, the biosynthesis of target proteins is disrupted. Therefore, there are at least two ways in which antisense agents act to effectively reduce the amount of pathogenic protein being synthesized – RNase H based degradation of RNA and prevention of ribosomal assembly and translation. This approach has a great advantage. It prevents a pathogenic protein from being produced, rather than trying to selectively neutralize it once it is made.

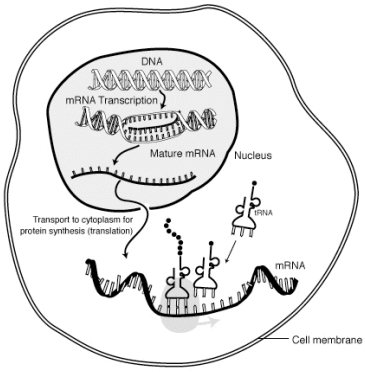

Figure: **DNA to Protein**: Role of messenger RNA in protein synthesis.

Antisense agents can be specifically targeted to genes that control expression of antibiotic resistance mechanisms, thereby potentially restoring an antibiotic-sensitive phenotype to the cell. A limiting factor in their potential application as therapeutic agents for bacterial infections is their poor uptake by bacterial cells. These agents have been successfully developed for the treatment of viral infections such as cytomegalovirus, hepatitis C, and HIV infections. The advantage of antisense therapy is that they can be manufactured fairly fast, they produce a lasting clinical effect, and they are highly specific to the target. Antisense agents also exhibit efficacy in broader clinical applications such as cancer therapy.

Key Points

- Antisense agents have broad applications in several diseases. Their use for treating microbial infections is promising.
- They are synthetic oligonucleotides that can be manufactured quickly and their biological effect is long-lasting.
- Their use for the treatment of antibiotic resistant bacterial infections is possible but limited by their poor uptake by the bacterial cell. Studies are being developed to improve their penetration into the cell.

Key Terms

- **messenger RNA**: RNA that encodes and carries information from DNA during transcription to sites of protein synthesis to undergo translation in order to yield a protein
- **nuclease**: Any of several enzymes capable of cleaving the phosphodiester bonds between the nucleotide subunits of nucleic acids.
- **hybridize**: To combine complementary subunits of multiple biological macromolecules.

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SECTION OVERVIEW

13.7: Antiviral Drugs

Topic hierarchy

13.7A: Antiviral Agents that Prevent Virus Uncoating or Release

13.7B: Antiviral DNA Synthesis Inhibitors

13.7C: Nucleotide and Nonnucleotide Reverse Transcriptase Inhibitors

13.7D: Protease Inhibitors

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13.7A: Antiviral Agents that Prevent Virus Uncoating or Release

Different approches are used to target the initial and final steps of a virus life cycle.

Learning Objectives

- Compare the mechanisms of the discussed antiviral drugs

Key Points

- The attachment step is targeted by molecules that will block the receptor on the host cell surface, or on the viral capsid region responsible for binding to the host receptor.
- Drugs that target the uncoating step bind to, and inactivate, proteins on the capsid surface responsible for the uncoating.
- The release step is targeted by drugs that inhibit the activity of neuraminidase, an enzyme on the viral surface.

Key Terms

- **sialic acid**: A derivative of neuraminic acid (a nine-carbon monosaccharide) that is often the sugar part of glycoproteins.

A viral infection starts with entry of the virus into the cell. The entry mechanism is complex, consists of multiple steps and involves host cell structures.

Targeting the Attachment Step

Virus infection starts with a virus attaching to the host cell by binding to a receptor molecule. There are two main strategies used to design antiviral drugs at this step:

- Using molecules that will bind to the cell receptor and inactivate it; thus preventing the virus from attachment. Examples include anti-receptor antibodies or natural ligands that can bind to the receptor.
- Using receptor-like molecules to bind to the virus and inactivate it before it meets the cell. These include anti-virus antibodies (with specificity against the viral structure that binds to the receptor) or synthetic molecules that mimic the receptor.

The search for such drugs, however, is very expensive and time-consuming.

Targeting the Uncoating Step

Another drug target is the uncoating step during viral infection. Uncoating is the process of capsid disintegration, which leads to the release of the genomic material. This step is performed by viral or host enzymes, or by capsid dissociation alone. Drugs that can perform such functions are used against the influenza virus, rhinoviruses (the cause of the common cold), and enteroviruses (gastrointestinal infections, meningitis, etc.). It is believed that such drugs prevent the virus from uncoating by blocking the proteins on the capsid responsible for uncoating, such as ion channel proteins. An example of such a drug is Rimantadine, which blocks the ion channel in the influenza virus. The ion channel has an important role in disintegrating the viral capsid.

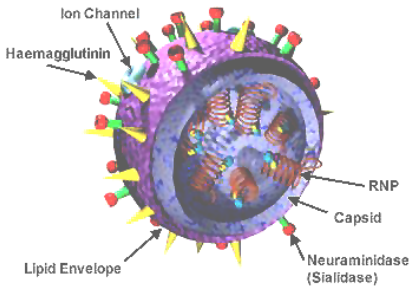

Figure: **Structure (3D) of the Influenza Virus**: The image depicts the major components of the virus structure, including the neuraminidase.

Targeting the Release of the Newly Formed Viral Particles

The last step in the virus life cycle—release from the cell—has been targeted by drugs as well. Neuraminidase is an enzyme on the capsid of influenza virus. It cleaves sialic acid from glycoproteins on the surface of the host cell and allows the viral particles to leave the cell. Tamiflu and Relenza are trend names of two drugs used to treat influenza infections by targeting neuraminidase.

Since viruses use many structures in the host cells to replicate, designing or discovering good antiviral drugs that will not affect the eukaryotic cells is a challenging task. Serious side effects are often observed with the use of antiviral drugs, as is resistance against the drugs. Developing drugs that inhibit different steps in the virus life cycle is of critical importance.

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13.7B: Antiviral DNA Synthesis Inhibitors

Inhibiting DNA synthesis during viral replication is another key approach in battling viral infections.

Learning Objectives

- Review the mechanism of action for antiviral DNA synthesis inhibitors and recognize the types of these inhibitors

Key Points

- Drugs such as acyclovir, are nucleoside analogues that lack a free 3′ group that is needed for the addition of the next nucleotide. When added into a growing DNA chain they stop its synthesis.
- Another drug, foscarnet, mimics pyrophosphates and inactivates the activity of the viral DNA polymerase.
- Resistance can develop against both of these groups of drugs.

Key Terms

- **CMV retinitis**: An inflammation of the eye's retina caused by CMV. It can lead to blindness.

Inhibiting DNA synthesis during viral replication is another approach to battle viral infections.

The most common strategy used for this approach is to use molecules that mimic the structure of a nucleoside. The similarity is good enough to ensure its incorporation into the newly synthesized DNA chain. However, the nucleoside analogue lacks free 3′ end needed for the addition of the next nucleotide. This prevents the incorporation of the next nucleotide and terminates the elongation of the DNA chain.

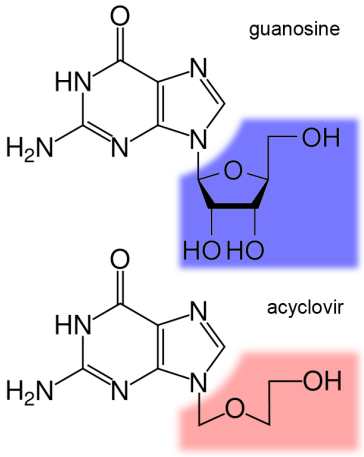

Figure: **Comparison of acyclovir and guanosine**: Acyclovir does not contain a sugar molecule with a 3′-OH group and will interrupt the synthesis of a newly synthesized nucleotide chain if added to it. The guanosine depicted in this specific image is used for RNA synthesis but acyclovir inhibits the synthesis of DNA synthesis.

One of the most often used antiviral drugs that works with the described mechanism is acyclovir (aciclovir), a guanosine analogue. It is used to treat herpes simplex virus infections (type 1 and type 2) as well as chicken pox and shingles. It was designed based on nucleosides isolated from a Caribbean sponge. After administration, the molecule gets activated by phosphorylation both by viral and host cell kinases and the resulting nucleotide incorporated into the newly synthesized DNA resulting in premature chain termination. The drug has very low cytotoxicity and there is low resistance to it.

Other drugs that are also nucleoside analogues and have the same mode of actions are ganciclovir (a synthetic analogue of 2′-deoxy-guanosine) and vidarabine(an adenosine analog). However, both drugs are more toxic and have more serious side effects than acyclovir.

Another type of drug that is a DNA synthesis inhibitor is foscarnet. It mimics pyrophosphate and inactivates the activity of the DNA polymerase. This inhibitor is active against the viral DNA polymerases at doses much lower than the ones needed to inhibit the human polymerases. This drug is used in cases of resistance against acyclovir and ganciclovir nucleoside analogue chemicals. It is also used to treat cytomegalovirus infection (CMV) and specifically CMV retinitis.

Another antiviral drug that targets DNA synthesis is hydroxycarbamide, commonly referred to as a hydroxyurea. Hydroxycarbamide can be used an antiretroviral drug against HIV/AIDS. The mechanism of hydroxycarbamide is thought to be based on the reduction of production of deoxyribonucleotides; therefore, inhibiting DNA synthesis. Hydroxycarbamide is thought to inhibit the enzyme ribonucleotide reductase.

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13.7C: Nucleotide and Nonnucleotide Reverse Transcriptase Inhibitors

Reverse transcriptase in viruses is inhibited by nucleoside (nucleotide) analogues or drugs that change the conformation of the enzyme.

Learning Objectives

- Summarize the mechanism of action for reverse transcriptase inhibitors

Key Points

- Nucleoside and nucleotide inhibitors are competitive substrate inhibitors that mimic the structure of a normal nucleotide but lack the 3′ hydroxyl group needed for the addition of the next nucleotide for DNA elongation.
- Non-nucleotide inhibitors bind to a site different than the active one and cause rearrangements of the protein domains needed for DNA polymerization.
- Mutations in the reverse transcriptase gene can cause resistance to both types of drugs.

Key Terms

- **competitive substrate inhibitors**: Molecules that bind to the active site of an enzyme and prevent the real substrate from binding to it.
- **non-competitive inhibitors**: Molecules that bind to sites other than the active site of an enzyme while still being able to indirectly inhibit its function.
- **nucleotide**: the monomer comprising DNA or RNA biopolymer molecules, consisting of a nitrogenous heterocyclic base; a five-carbon pentose sugar; and a phosphate group

Reverse transcriptase is an enzyme that has the ability to transcribe single-stranded DNA from a single-stranded RNA chain. This is the reverse of the usual flow of information when RNA is synthesized from DNA. Viruses that use reverse transcriptase to convert their genetic material (RNA) into DNA are called retroviruses. One of the most prominent representative of a retrovirus is HIV. Due to the high prevalence of HIV/AIDS in the world, it is important to have drugs that will prevent or cure the infection. This enzyme is also found in tumors and cancer cells.

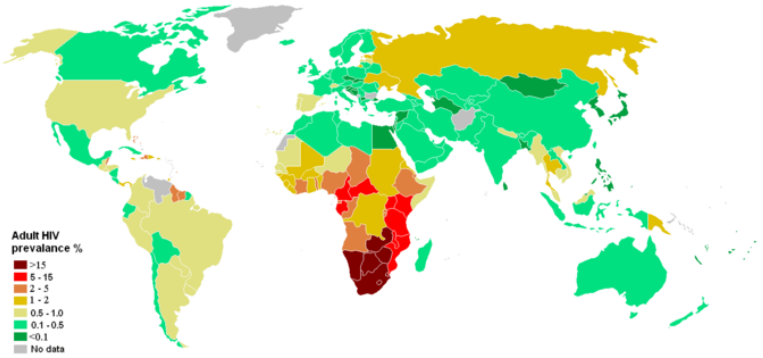

Figure: **Estimation of adults with HIV/AIDS by country**: The data shows the people, between 18-49 years, by country who are affected by HIV/AIDS. The information is provided by UNAIDS based on a report from July 2008

Drugs that inhibit the function of this enzyme are divided into three groups:

- nucleoside analog reverse transcriptase inhibitors
- nucleotide analog reverse transcriptase inhibitors
- non-nucleoside reverse transcriptase inhibitors

The first two inhibitors act on the same principle. They mimic, respectively, nucleosides or nucleotides but lack a free hydroxyl group at the 3′ end. The major difference between them is that the nucleosides need to be phosphorylated by cellular kinases. The enzyme reverse transcriptase recognizes them as regular nucleotides and inserts them into the newly synthesized DNA chain. But once inserted the elongation stops at them because no more nucleotides can be added due to the lack of the 3′ hydroxyl group and the inability of the formation of 5′-3′ phosphodiester bond. This process is called chain termination. Nucleoside and nucleotide inhibitors are also called competitive substrate inhibitors. Examples of such drugs are Zidovudine (AZT) and Lamivudine. AZT was the first FDA approved drug for the treatment of HIV. Lamivudine is used for the treatment of both HIV and hepatitis B. Since

some viruses, such as hepatitis B, carry RNA-dependent DNA polymerases reverse transcriptase inhibitors can be used to treat these infections as well.

Non-nucleotide reverse transcriptase inhibitors bind to a different site, not the active one, of the reverse transcriptase enzyme. That leads to conformational changes that distort the position of the DNA binding sites in the enzyme and lead to halt in DNA polymerization. Non-nucleotide inhibitors are non-competitive inhibitorsof reverse transcriptase. Such drugs are Efavirenz and Nevirapine.

Resistance occurs to all drug groups. The mechanisms for resistance against the nucleoside (nucleotide) inhibitors are two. The first one is due to mutations in the N-terminal polymerase domain of the reverse transcriptase that makes it less likely to incorporate the analogues. The second mechanism is caused by mutations in the transcriptase that allow the removal of the incorporated inhibitor and hence restart of DNA replication.

Resistance to the non-nucleotide inhibitors is caused by mutations in the inhibitor binding site of the enzyme. Such mutations prevent the binding of the inhibitor to the enzyme.

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13.7D: Protease Inhibitors

Protease inhibitors target viral proteases which are key enzymes for the completion of viral maturation.

Learning Objectives

- Describe the mechanism of action for protease inhibitors

Key Points

- Protease inhibitors mimic peptides or are chemicals that can be inserted in the active site of a protease. They prevent it from binding the viral polyproteins.
- Such drugs were one of the first to be used against HIV. They are an inseparable part of the HIV/AIDS therapy.
- Mutations in the enzyme active site and other sites, which cause conformational changes, can cause resistance.

Key Terms

- **cross-resistance**: Bacterial or viral resistance to a chemical which causes resistance to other chemicals of the same group.

Proteases are enzymes that have the ability to cut proteins into peptides. They are used by some viruses (e.g., HIV) to cleave precursor long protein chains into individual proteins. This allows the completion of the assembly step in the viral life cycle where the proteins and the viral RNA come together to form virion particles ready to exit the cell.

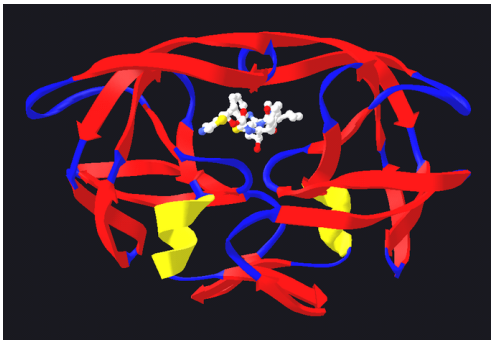

Figure: **HIV protease with bound protease inhibitor**: The drug is ritonavir depicted here with a white molecule in the middle of the enzyme structure.

The design of protease inhibitors, that could be used to battle HIV, started soon after the discovery of the virus. The first approved protease inhibitor drug was released on the market in 1995, only 10 years after the discovery of HIV. These drugs are an inseparable part of an HIV therapy. Natural protease inhibitors are found in Shiitake mushrooms. The experimental protease inhibitor drugs Zmapp and Brincidofovir are currently being tested to treat the ebola virus disease.

Protease inhibitors are short peptide-like molecules that are competitive inhibitors of the enzyme. Instead of -NH-CO- peptide link, they contain -(CH_2-CH(OH)-). When such a peptide gets into the enzyme active site, the protease is unable to cut the linkage and gets inactivated. This leads to a lack of cleavage of the polypeptide chains of two crucial viral proteins, Gag and Pol, which are essential structural and enzymatic proteins of HIV. Their absence blocks the formation of mature virion particles.

Saquinavir is the first clinically used peptide-like inhibitor. Some protease inhibitors do not mimic peptides in their structure. One such drug is *Nelfinavir*. In general, protease inhibitors exhibit the unusual side effect of fat storage in non-typical organs and tissues. The reasons for this are still unclear.

Mutations in the enzyme active site and other sites, which cause conformational changes, can cause resistance. Quite often one mutation can lead to resistance to many different drugs simultaneously since they all share the same mode of action. This is called cross-resistance. It is one of the major drawbacks of protease inhibitors therapy.

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SECTION OVERVIEW

13.8: Other Antimicrobial Drugs

Topic hierarchy

13.8A: Antifungal Drugs

13.8B: Antiprotozoan and Antihelminthic Drugs

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13.8A: Antifungal Drugs

Learning Objectives

- Compare and contrast the mechanisms of action for: polyene, azole,allylamine and echinocandin antifungals

The field of mycology deals with the study of fungi and has resulted in the identification of over 60,000 species of fungi. Fungi are classified as eukaryotic organisms which are primarily classified based on spore production. The classification and identification of a species of fungi by spore class, in combination with the basic biological mechanism(s) it uses to sustain life, is key in developing anti-fungal drugs.

The development of antifungal drugs focuses on the classes of mycotic diseases for which fungi are responsible. These classes include hypersensitivity—allergic reactions based on the presence of mold and spores; mycotoxicoses—diseases based on the presence of fungi that produce toxins in animal feed and human food products; mycetismus—mushroom poisoning; and lastly, mycoses—characterized by infection.

Disease-causing fungi are targeted and then drug classes are classified based on drug structure or mechanism. Some of the major classes of antifungal medication include polyene antifungals, azole antifungals, allylamines, and echinocandins. It is important to note that antifungal drugs are not limited to these classes, as there are additional drugs capable of targeting fungi that do not fall into these categories.

Polyene Antifungals

Polyene antifungals are characterized by the presence of multiple conjugated double bonds in the drug structure. This specific antifungal drug class targets the fungal cell membrane. The target sterol is ergosterol, which is specific to fungi cell membranes; in animal cell membranes cholesterol is the key sterol. The fungal cell membrane becomes leaky, resulting in movement of essential cellular contents, such as organic molecules and ions, out of the cell. Amphotericin B is an example of a polyene antifungal; it is selective for ergosterol and can be used as a broad spectrum drug administered intravenously.

Azole Antifungals

Azole antifungals are characterized by the ability to inhibit ergosterol synthesis in fungal membranes. The biosynthesis of ergosterol requires the enzyme lanosterol 14 α-demethylase. This enzyme is needed to convert lanosterol to ergosterol. Targeting this enzyme prevents ergosterol production. Thus, the fungal membrane structure is depleted of ergosterol and the fungus dies. The various types of azole classified drugs include imidazole, triazole and thiazole antifungals. Azole drugs are broad-spectrum drugs and treat fungal infections of the skin or mouth. An example of an azole drug is Clotrimazole, commonly used to treat athlete's foot, ringworm, vaginal yeast infections, and oral thrush.



Figure: **Ringworm**: Ringworm on a human leg.

Allylamine Antifungals

Allylamine antifungals are characterized by the ability to inhibit fungal squalene metabolism. The biosynthesis of ergosterol requires an enzyme called squalene peroxidase. Squalene peroxidase is responsible for catalyzing the first step in ergosterol biosynthesis; inhibition of this enzyme results in disruption of ergosterol synthesis. The inhibition of squalene metabolism is toxic to the fungi because of the buildup of squalene and the inhibition of ergosterol synthesis. An example of an allylamine drug is Terbinafine, which is commonly used to treat fungal skin infections.

Echinocandin Antifungals

Echinocandins are characterized by their ability to inhibit synthesis of a key component of the *fungal cell wall*, while previously discussed drugs target the *fungal cell membrane*. Cell wall synthesis requires the production of glucan by the enzyme 1,3-β glucan synthase. Echinocandins specifically inhibit glucan synthesis by targeting that enzyme. This class of drug is most effective when administered by injection, as it is poorly absorbed when administered orally. Echinocandin injection allows the drug to treat a systemic infection of the sort typically seen in immunocompromised patients. An example of an echinocandin based drug is Caspofungin. Caspofungin blocks cell-wall synthesis by disrupting glucan synthesis; it can target invasive candidiasis and aspergillus.

Additional Antifungal Drugs

The major classes of antifungal drugs are discussed above are not the only drugs capable of effectively targeting fungi. The emergence of alternative medicine as a hot field of research has also increased the list of available antifungal compounds. For example, numerous compounds and essential oils found in nature have been found to have antifungal properties that could be utilized for treatment. Examples of these include coconut oil, orange oil, olive leaf, and zinc.

The identification of additional antifungal compounds is key to the development of drugs that can replace existing drugs to which fungi have developed resistance. The discovery process for effective and fungi-specific drugs is enduring and laborious, as the drugs must be specific for fungi cells. However, with the expansion of molecular studies in fungal organisms, the opportunity to identify novel and fungal specific mechanisms will allow for the development of new drugs.

Key Points

- The various classes of antifungal drugs exploit the unique fungal structure.
- The synthesis of both cell membrane and cell wall components are key targets for antifungal drugs.
- Classes of antifungal medications include: polyene antifungals, azole drugs, allylamines and echinocandins.

Key Terms

- **ergosterol**: major component of fungal cell membranes.
- **mycology**: the study of fungi

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13.8B: Antiprotozoan and Antihelminthic Drugs

Antiprotozoan and antihelminthic drugs are characterized based on structure and the mechanism of action by which they target the organism.

Learning Objectives

- Describe the objective of drugs against helminths anf the disadvantages to developing drugs against protozoa

Key Points

- Antiprotozoan drugs are typically species specific.
- It is essential that antiprotozoan drugs target pathways and mechanisms specific to protozoa as overlap in the basic biology can result in inaccurate targeting of the drug to both the host and protozoa.
- Antihelminthic drugs typically focus on the disruption of structural mechanisms that maintain body structure resulting in paralysis of the helminth which promotes expulsion.

Key Terms

- **helminth**: A parasitic roundworm or flatworm.
- **protozoa**: Protozoa are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior, e.g., movement. Protozoa were regarded as the partner group of protists to protophyta, which have plant-like behavior, e.g., photosynthesis.
- **Parasite**: Parasitism is a non-mutual relationship between organisms of different species where one organism, the parasite, benefits at the expense of the other, the host.

Parasites are organisms that live on or in a host organism to obtain food. Two major classes of parasitic organisms include protozoa and helminths.

Protozoa are unicellular eukaryotic organisms that are classified as either free-living or parasitic organisms. Protozoa are further classified based on their mode of locomotion and include: Sarcodina (amoeba); Mastigophora (flagellates); Ciliophora (ciliates); and Sporozoa (non motile in adult form). Some examples of diseases caused by protozoa include: Malaria, Giardia, Trichomoniasis, and Leishmaniasis.

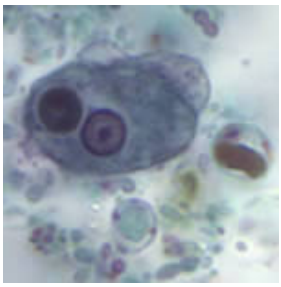

Figure: **Entamoeba histolytica**: Entamoeba histolytica is classified as a protozoa, specifically a Sarcodina.

Helminths are multicellular eukaryotic organisms that are also classified as either free-living or parasitic chemoheterotrophic organisms. Helminths are parasitic worms and are divided into three major groups including: flatworms (platyhelminths); thorny-headed worms (acanthocephalins); and roundworms (nematodes and hookworms).



Figure: **Hookworms**: Hookworms attached to the intestinal mucosa.

The variation that exists between protozoa contributes to complications associated with developing effective drugs. The lack of similarities between protozoans demands the need for highly specific drugs and medications against individual pathogens. In addition, protozoa are eukaryotic and exhibit similar properties and metabolic pathways as human cells. Therefore, the drugs that are developed to target protozoans are classified by either their mechanism of action or the organism for which they target. In terms of mechanism of actions, most antiprotozoan drugs specifically target the organism to prevent its growth and reproduction.

Protozoal diseases can also be prevented by targeting the route of transmission and/or targeting vector organisms. For example, Malaria is caused by the protozoan Plasmodia. This parasite is injected into humans via mosquitoes. The development of antimalarial drugs are based on the life cycle of Plasmodiain both the mosquito and human host.

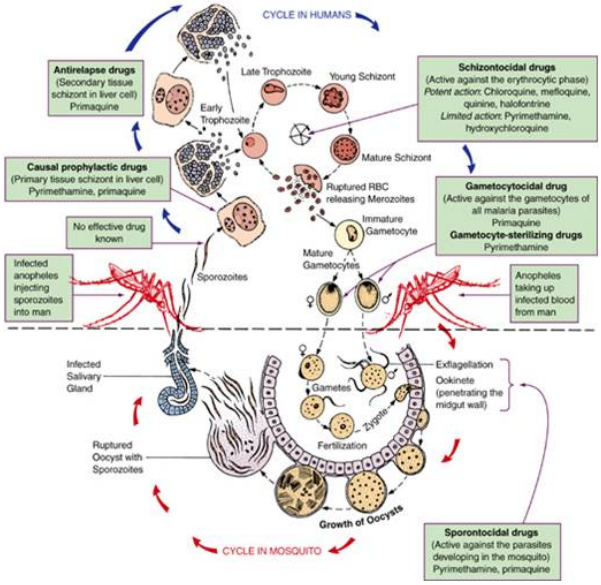

Figure: **Life Cycle of Plasmodium**: Malaria, a protzoan based disease, is transmitted via an arthropod vector. The development of antimalarial drugs focuses on the life cycle in both the mosquito and human hosts.

Other types of antiprotozan drugs specifically target metabolic mechanisms utilized by the parasite. For example, African sleeping sickness is caused by trypanosomes. The drug Eflornithine attacks this parasite by targeting an enzyme responsible for regulating cell division.

Helminths are characterized as various types of parasitic worms, which are effectively targeted by promoting expulsion from the body. Parasitic helminths worms include: tapeworms, flukes, leeches and hookworms. The drugs utilized to target helminths are characterized based on chemical structure and mechanism of action. A few examples of the major drug classes include: piperazine, benzimidazole, levamisole, pyrantel, morantel and emodepside.

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CHAPTER OVERVIEW

14: Pathogenicity

Pathogenicity refers to the ability of an organism to cause disease (ie, harm the host). This ability represents a genetic component of the pathogen and the overt damage done to the host is a property of the host-pathogen interactions. Commensals and opportunistic pathogens lack this inherent ability to cause disease.

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  - 14.1A: Portals of Microbe Entry
  - 14.1B: Colonization and Growth
  - 14.1C: Pathogenicity Islands and Virulence Factors
  - 14.1D: Adherence
  - 14.1E: Host Risk Factors
  - 14.1F: Innate Resistance
- 14.2: Overview of Microbe-Host Interactions
  - 14.2A: Normal Microbiota and Host Relationships
  - 14.2B: Opportunistic Microorganisms
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- 14.3: Penetrating Host Defenses
  - 14.3A: Penetrating Host Defenses
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- 14.4: Damaging Host Cells
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  - 14.6C: Helminths
  - 14.6D: Algae

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SECTION OVERVIEW

14.1: Entry into the Host

Topic hierarchy

14.1A: Portals of Microbe Entry

14.1B: Colonization and Growth

14.1C: Pathogenicity Islands and Virulence Factors

14.1D: Adherence

14.1E: Host Risk Factors

14.1F: Innate Resistance

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14.1A: Portals of Microbe Entry

Microbes gain access to human tissues via mucosal surfaces within the body or epithelial surfaces on the outside of the body.

Learning Objectives

- Recognize the various methods and types of microorganism transmission: vectors, hosts, horizontal, vertical transmissions

Key Points

- Transmission can be direct (vertically or horizontally) or indirect.
- Infectious agents are generally specialized for a particular method of transmission.
- A locus is the point on the body where a pathogen enters.

Key Terms

- **infectious**: Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.
- **contagious**: Of a person, having a disease that can be transmitted to another person by touch.

Microbes gain access to human tissues via two main types of routes: mucosal surfaces within the body (linings of the respiratory, digestive, reproductive, or urinary tracts) or epithelial surfaces on the outside of the body (areas of skin that are either undamaged or compromised due to insect bites, cuts/scrapes, or other wounds).

Transmission of Microorganisms

Transmission of microorganisms occurs directly from one person to another by one or more of the following means:

- droplet contact by coughing or sneezing on another person
- direct physical contact by touching an infected person
- direct physical contact (usually by touching soil contamination or a contaminated surface)
- airborne transmission (if the microorganism can remain in the air for long periods)
- fecal-oral transmission (usually from contaminated food or water sources)
- contamination via intravenous drug us
- contamination from blood given via transfusion or organ transplants

Transmission can also be indirect via another organism, either a vector (like a mosquito) or an intermediate host (like how a tapeworm from a pig can be transmitted to humans who ingest improperly cooked pork).

Horizontal or Vertical Transmission

Disease can also be directly transmitted in two ways: horizontally or vertically. Horizontal disease transmission occurs from one individual to another in the same generation (peers in the same age group), and can occur by either direct contact (licking, touching, biting), or indirect contact. Vertical disease transmission involves passing a disease causing agent vertically from parent to offspring.

Pathogens must have a way to be transmitted from one host to another to ensure their species ‘ survival. Infectious agents are generally specialized for a particular method of transmission. Taking an example from the respiratory route, from an evolutionary perspective a virus or bacteria that causes its host to develop coughing and sneezing symptoms has a great survival advantage: it is much more likely to be ejected from one host and carried to another.

A locus is the point on the body where a pathogen enters. In droplet contact and other airborne transmission it is generally the respiratory system through the nose, mouth, or eye surfaces. In direct physical and indirect contact it is generally through a wound in the skin or through a mucous membrane. In fecal-oral transmission, it is through the mouth. In vector-borne transmission, it is at the bite or sting of the vector. Other common indirect routes include contaminated food or water.

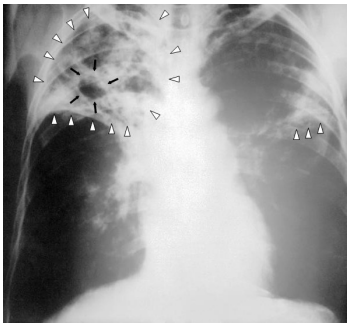

Figure: **Chest x-ray of a patient with tuberculosis.**: In this chest X-ray of a person with advanced tuberculosis, the infections in both lungs are marked by white arrowheads and the formation of a cavity is marked by black arrows. The boundary between contagious and non-contagious infectious diseases is not perfectly drawn, as illustrated by tuberculosis, which is clearly transmissible from person to person, but was not classically considered a contagious disease.

Sexual Transmission

In sexual transmission, infection originates directly between surfaces in contact during intercourse (the usual route for bacterial infections and those infections causing sores) or from secretions (semen or the fluid secreted by the excited female). Sexually transmitted diseases such as HIV and Hepatitis B are thought to be transmitted through unprotected sexual intercourse (including anal and oral routes), contaminated blood transfusions, sharing hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Bodily fluids such as saliva and tears do not transmit HIV. Oral sexual practices have increased the incidence of herpes simplex virus 1 (which is usually responsible for oral infections) in genital infections and the increased incidence of the type 2 virus (more common genitally) in oral infections. Herpes diseases that are transmitted primarily by oral means may be caught through direct contact with an infectious area of the skin.

Direct Contact: Contagious Diseases

Diseases that can be transmitted by direct contact are called contagious (contagious is not the same as infectious). Although all contagious diseases are infectious, not all infectious diseases are contagious. Interestingly, some contagious diseases like tuberculosis were not classically considered to be contagious even though they are transmissible from person to person. Direct transmission can also occur by sharing a towel (where the towel is rubbed vigorously on both bodies) or items of clothing in close contact with the body (socks, for example) if they are not washed thoroughly between uses. Some diseases that are transmissible by direct contact include Athlete's foot and impetigo.

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14.1B: Colonization and Growth

Infection begins when an organism successfully colonizes a host by entering the host's body, growing and multiplying from there.

Learning Objectives

- Distinguish between colonization and infection

Key Points

- Some virulent bacteria produce special proteins that allow them to colonize parts of the host body.
- Wound colonization refers to nonreplicating microorganisms within the wound, while in infected wounds replicating organisms exist and tissue is injured.
- While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs.

Key Terms

- **infection**: An uncontrolled growth of harmful microorganisms in a host.

Infection begins when an organism successfully colonizes by entering the body, growing and multiplying from there. Most humans are not easily infected. Those who are weak, sick, malnourished, have cancer or are diabetic possess an increased susceptibility to chronic or persistent infections. Individuals who have a suppressed immune system are particularly susceptible to opportunistic infections.

Entrance to the host generally occurs through the mucosa in orifices like the oral cavity, nose, eyes, genitalia, anus, or open wounds. While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs. Some pathogens grow within the host cells (intracellular) whereas others grow freely in bodily fluids. Some virulent bacteria produce special proteins that allow them to colonize parts of the host body. Helicobacter pylori is able to survive in the acidic environment of the human stomach by producing the enzyme urease. Colonization of the stomach lining by this bacterium can lead to gastric ulcer and cancer. The virulence of various strains of Helicobacter pylori tends to correlate with the level of production of urease.

Wound colonization refers to nonreplicating microorganisms within the wound, while in infected wounds replicating organisms exist and tissue is injured. All multicellular organisms are colonized to some degree by extrinsic organisms and the vast majority of these exist in either a mutualistic or commensal relationship with the host. An example of the former is the anaerobic bacteria species, which colonizes the mammalian colon, and an example of the latter is various species of staphylococcus that exist on human skin. Neither of these colonizations are considered infections.

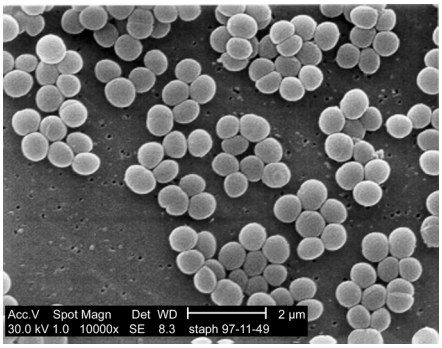

Figure: **Staphylococcus aureus**: Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.

The difference between an infection and a colonization is often only a matter of circumstance. Non-pathogenic organisms can become pathogenic given specific conditions and even the most virulent organism requires certain circumstances to cause a compromising infection. Some colonizing bacteria, such as Corynebacteria sp. and viridans streptococci, prevent the adhesion and colonization of pathogenic bacteria. They thus have a symbiotic relationship with the host, preventing infection and speeding wound healing.

The variables involved in the outcome of a host becoming inoculated by a pathogen and the ultimate outcome include: the route of entry of the pathogen and the access to host regions that it gains, the intrinsic virulence of the particular organism, the quantity or

load of the initial inoculant, and the immune status of the host being colonized. As an example, the Staphylococcus species remains harmless on the skin. But when present in a normally sterile space, such as in the capsule of a joint or the peritoneum the Staphylococcus species multiplies without resistance and creates a burden on the host.

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14.1C: Pathogenicity Islands and Virulence Factors

Pathogenicity islands (PAIs) are a distinct class of genomic islands acquired by microorganisms through horizontal gene transfer.

Learning Objectives

- Describe the traits characterizing a pathogenicity island and its advantages

Key Points

- Pathogenicity islands are discrete genetic units flanked by direct repeats, insertion sequences or tRNA genes, which act as sites for recombination into the DNA.
- PAIs are incorporated in the genome of pathogenic organisms, but are usually absent from those nonpathogenic organisms of the same or closely related species.
- PAIs carry genes encoding one or more virulence factors, including, but not limited to, adhesins, toxins, or invasins.

Key Terms

- **pathogenicity island**: A distinct class of genomic islands acquired by microorganisms through horizontal gene transfer.
- **virulence factor**: Molecules expressed and secreted by pathogens (bacteria, viruses, fungi and protozoa) that enable them to achieve colonization of a niche in the host, immunoevasion, immunosuppression, entry into and out of the cells, and obtaining nutrition from the host.

Pathogenicity Islands and Virulence Factors

Pathogenicity islands (PAIs) are a distinct class of genomic islands acquired by microorganisms through horizontal gene transfer. They are incorporated in the genome of pathogenic organisms, but are usually absent from those nonpathogenic organisms of the same or closely related species. These mobile genetic elements may range from 10-200 kb, and may encode genes contributing to the virulence of the respective pathogen. Typical examples are adherence factors, toxins, iron uptake systems, invasion factors and secretion systems.

Pathogenicity islands are discrete genetic units flanked by direct repeats, insertion sequences or tRNA genes, which act as sites for recombination into the DNA. Cryptic mobility genes may also be present, indicating the provenance as transduction.

One species of bacteria may have more than one PAI (i.e. salmonella has at least five). PAIs are transferred through horizontal gene transfer events such as transfer by a plasmid, phage, or conjugative transposon. PAIs carry genes encoding one or more virulence factors, including, but not limited to, adhesins, toxins, or invasins. They may be located on a bacterial chromosome or may be transferred within a plasmid. The GC-content of pathogenicity islands often differs from that of the rest of the genome, potentially aiding in their detection within a given DNA sequence.

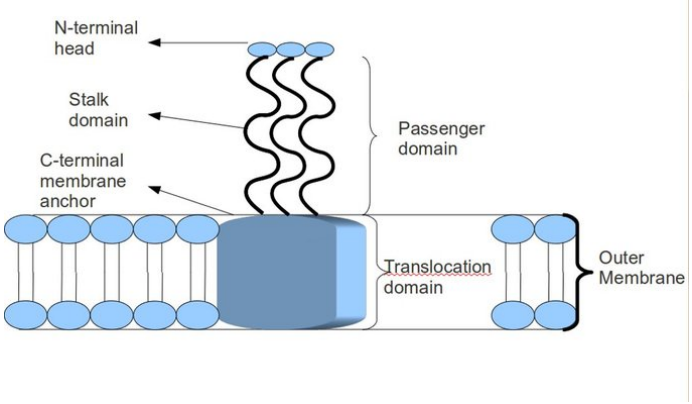

Figure: **Trimeric Autotransporter Adhesin structure**: The structure on the top (outside) of the outer membrane is a TAA protein. Various parts of the TAA are labelled, including the N-terminal head, stalk domain and C-terminal membrane anchor.

PAIs are flanked by direct repeats; the sequence of bases at two ends of the inserted sequence are the same. They carry functional genes such as integrases, transposases, or part of insertion sequences, to enable insertion into host DNA. PAIs are often associated with tRNA genes, which target sites for this integration event. They can be transferred as a single unit to new bacterial cells, thus conferring virulence to formerly benign strains.

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14.1D: Adherence

Adhesins are cell-surface components or appendages of bacteria that facilitate bacterial adhesion to other cells or to inanimate surfaces.

Learning Objectives

- Review the role of adhesins, including fimbriae and the Dr family, in pathogenic bacteria

Key Points

- Adhesins are a type of virulence factor.
- Adherence is an essential step in bacterial pathogenesis or infection, required for colonizing a new host.
- Fimbriae are believed to be involved in attachment to solid surfaces or to other cells and are essential for the virulence of some bacterial pathogens.

Key Terms

- **adhesin**: Any of several factors that enable bacteria to adhere to epithelial surfaces as a step towards infection.
- **fimbriae**: Fine filaments of protein distributed over the surface of bacteria that are believed to be involved in attachment to solid surfaces or to other cells, and are essential for the virulence of some bacterial pathogens.

Adhesins are cell-surface components or appendages of bacteria that facilitate bacterial adhesion or adherence to other cells or to inanimate surfaces. Adhesins are a type of virulence factor. Adherence is an essential step in bacterial pathogenesis or infection, required for colonizing a new host. For example, nontypeable Haemophilus influenzae expresses the adhesins Hia, Hap, Oap, and a hemagglutinating pili.

Fimbriae are fine filaments of protein, just 3–10 nanometers in diameter and up to several micrometers in length. They are distributed over the surface of the cell, and resemble fine hairs when seen under the electron microscope. Fimbriae are believed to be involved in attachment to solid surfaces or to other cells, and are essential for the virulence of some bacterial pathogens. Most fimbriae of Gram-negative bacteria function as adhesins, but in many cases the actual adhesin is a minor subunit protein at the tip of the fimbriae. In Gram-positive bacteria, a protein or polysaccharide surface layer serves as the specific adhesin. To effectively achieve adherence to host surfaces, many bacteria produce multiple adherence factors called adhesins.

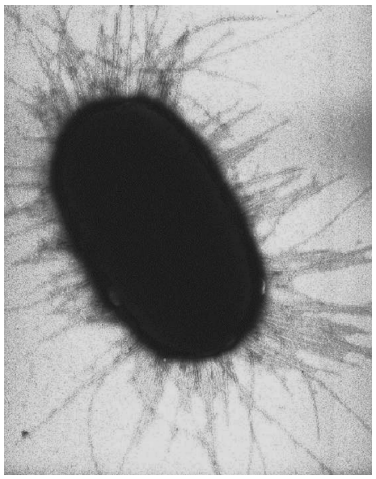

Figure: **E. coli fimbriae**: In bacteriology, a fimbria (plural fimbriae; abbreviated FIM) is an appendage composed of curlin proteins that can be found on many Gram-negative and some Gram-positive bacteria that is thinner and shorter than a flagellum. This appendage ranges from 3-10 nanometers in diameter and can be up to several micrometers long.

The Dr family of adhesins bind to the Dr blood group antigen component of decay-accelerating factor (DAF). These proteins contain both fimbriated and afimbriated adherence structures and mediate adherence of uropathogenic Escherichia coli to the urinary tract. They do so by inducing the development of long cellular extensions that wrap around the bacteria. They also confer the mannose-resistant hemagglutination phenotype, which can be inhibited by chloramphenicol. The N-terminal portion of the mature protein is thought to be responsible for chloramphenicol sensitivity. Also, they induce activation of several signal

transduction cascades, including activation of PI-3 kinase. The Dr family of adhesins are particularly associated with cystitis and pregnancy-associated pyelonephritis.

Adhesins are attractive vaccine candidates because they are often essential to infection and are surface-located, making them readily accessible to antibodies. The effectiveness of anti-adhesin antibodies is illustrated by studies with FimH, the adhesin of uropathogenic Escherichia coli (UPEC). In animal models, passive immunization with anti FimH-antibodies and vaccination with the protein significantly reduced colonization by UPEC. Moreover, the Bordetella pertussis adhesins FHA and pertactin are components of 3 of the 4 acellular pertussis vaccines currently licensed for use in the U.S.

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14.1E: Host Risk Factors

Individuals who are weak, sick, malnourished, have cancer, or are diabetic have increased susceptibility to chronic or persistent infections.

Learning Objectives

- Recognize the risk factors that increase chance of disease

Key Points

- Risk of infection is a nursing diagnosis; “the state in which an individual is at risk to be invaded by an opportunistic or pathogenic agent (virus, fungus, bacteria, protozoa, or other parasite) from endogenous or exogenous sources” is the diagnostic definition of risk.
- Examples of risk factors includes decreased immune system secondary to disease, compromised circulation secondary to peripheral vascular disease, compromised skin integrity secondary to surgery, or repeated contact with contagious agents.
- Techniques like hand washing, wearing gowns, and wearing face masks can help prevent infections from being passed from the surgeon to the patient or vice versa.

Key Terms

- **opportunistic infection**: Any infection that causes disease and occurs only when the host’s immune system is impaired.
- **colitis**: inflammation of the colon.
- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.

Most humans are not easily infected. Those who are weak, sick, malnourished, have cancer, or are diabetic have increased susceptibility to chronic or persistent infections. Individuals who have a suppressed immune system or who are on immunosuppressive drugs are particularly susceptible to opportunistic infections.

Risk of infection is a nursing diagnosis which is defined as “the state in which an individual is at risk to be invaded by an opportunistic or pathogenic agent (virus, fungus, bacteria, protozoa, or other parasite) from endogenous or exogenous sources. ” The risk of infection depends on a number of endogenous sources. Skin damage from incision can increase a patient’s risk of infection, as can very young or old age, due to a naive or compromised immune system respectively. Examples of risk factors include decreased immune system resulting from disease, compromised circulation caused by peripheral vascular disease, compromised skin integrity as a result of surgery, or repeated contact with contagious agents.

Risk Reduction

Techniques like hand washing, wearing gowns, and wearing face masks can help prevent infections from being passed between the surgeon and the patient. Frequent hand washing remains the most important defense against the spread of unwanted organisms. Good nutrition is necessary to reduce risk. So is a healthy lifestyle. By avoiding illicit drugs, using a condom, and entering an exercise program one can improve one’s risk factors. Foods should be cooked to recommended temperatures; avoid foods that have been left outside for long. One should not take antibiotics for longer than needed or when they are not needed—long term use of antibiotics leads to resistance and increased the chance of developing opportunistic infections like clostridium difficile colitis. Vaccination is another vital means of preventing infections by encouraging the development of immune resistance in vaccinated hosts.

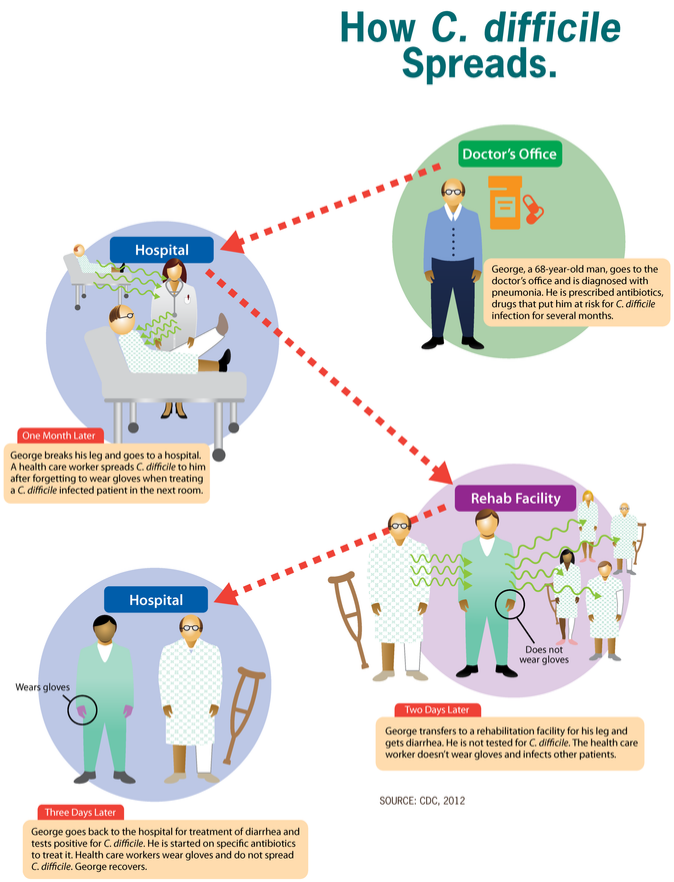

Figure: **How C. difficile spreads**: C. difficile is transmitted from person to person by the fecal-oral route. The organism forms large numbers of heat-resistant spores. These are not killed by alcohol-based hand cleansers or routine cleaning of surfaces. These spores remain viable in the hospital or nursing home environment for long periods of time. Because of this, the bacteria can be cultured from almost any surface in the hospital. Once spores are ingested by a patient, they pass through the stomach unscathed because of their acid-resistance. They germinate into vegetative cells in the colon upon exposure to bile acids, and multiply.

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14.1F: Innate Resistance

Several barriers protect organisms from infection including mechanical, chemical, and biological barriers.

Learning Objectives

- Discuss the various innate barriers within humans that provide protection from infection

Key Points

- The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.
- The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts.
- Some of these organisms perform tasks that are useful for the human host, but the majority have no known beneficial or harmful effect.

Key Terms

- **lysozyme**: A bacteriolytic (or antibiotic) enzyme found in many animal secretions and in egg white.
- **microbiota**: The microbial flora harbored by normal, healthy individuals.
- **flora**: the microorganisms that inhabit some part of the body, such as intestinal flora

Several barriers protect organisms from infection, including mechanical, chemical, and biological barriers. However, as organisms cannot be completely sealed against their environments, other systems act to protect body openings such as the lungs, intestines, and the genitourinary tract. In the lungs, coughing and sneezing mechanically eject pathogens and other irritants from the respiratory tract. The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.

Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides such as the β-defensins. Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are also antibacterials. Vaginal secretions serve as a chemical barrier following menarche, when they become slightly acidic, while semen contains defensins and zinc to kill pathogens. In the stomach, gastric acid and proteases serve as powerful chemical defenses against ingested pathogens. Within the genitourinary and gastrointestinal tracts, commensal flora serve as biological barriers by competing with pathogenic bacteria for food and space and, in some cases, by changing the conditions in their environment, such as pH or available iron. This reduces the probability that pathogens will reach sufficient numbers to cause illness. However, since most antibiotics non-specifically target bacteria and do not affect fungi, oral antibiotics can lead to an “overgrowth” of fungi and cause conditions such as a vaginal candidiasis (a yeast infection). There is good evidence that re-introduction of probiotic flora, such as pure cultures of the lactobacilli normally found in unpasteurized yogurt, helps restore a healthy balance of microbial populations in intestinal infections in children and encouraging preliminary data in studies on bacterial gastroenteritis and inflammatory bowel diseases. Inflammation is one of the first responses of the immune system to infection.

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect. Those that are expected to be present, and that under normal circumstances do not cause disease, but instead participate in maintaining health, are deemed members of the normal flora.

Populations of microbes (such as bacteria and yeasts) inhabit the skin and mucosa. Their role forms part of normal, healthy human physiology. However, if microbe numbers grow beyond their typical ranges (often due to a compromised immune system) or if microbes populate atypical areas of the body (such as through poor hygiene or injury), disease can result.

Many of the bacteria in the digestive tract are collectively referred to as the gut flora. In this context, *gut* is synonymous with intestinal, and *flora* with microbiota and microflora, the word microbiome is also in use. They are able to break down certain nutrients such as carbohydrates that humans otherwise could not digest. The majority of these commensal bacteria are anaerobes, meaning they survive in an environment with no oxygen. Normal flora bacteria can act as opportunistic pathogens at times of lowered immunity.

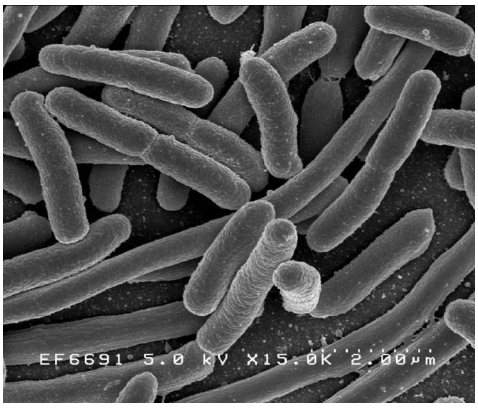

Figure: **Gut Flora**: Gut flora consists of microorganisms such as Escherichia Coli that live in the digestive tracts of animals. It is the largest reservoir of human flora. In this context, gut is synonymous with intestinal, and flora with microbiota and microflora. The word microbiome is also in use.

Archaea are present in the human gut, but, in contrast to the enormous variety of bacteria in this organ, the numbers of archaeal species are much more limited. Fungi, in particular yeasts, are present in the human gut. The best-studied of these are Candida species. This is because of their ability to become pathogenic in immune compromised hosts. Yeasts are also present on the skin, particularly Malassezia species, where they consume oils secreted from the sebaceous glands.

A small number of bacteria are normally present in the conjunctiva. Staphylococcus epidermidis and certain coryneforms such as Propionibacterium acnes are dominant. The lachrymal glands continuously secrete, keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material. Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.

The gut flora is the human flora of microorganisms that normally live in the digestive tract and can perform a number of useful functions for their hosts. Though people can survive with no gut flora, the microorganisms perform a host of useful functions such as fermenting unused energy substrates, training the immune system, preventing growth of harmful species, regulating the development of the gut, producing vitamins for the host (such as biotin and vitamin K), and producing hormones to direct the host to store fats. However, in certain conditions, some species are thought to be capable of causing disease by causing infection or increasing cancer risk for the host.

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SECTION OVERVIEW

14.2: Overview of Microbe-Host Interactions

Topic hierarchy

14.2A: Normal Microbiota and Host Relationships

14.2B: Opportunistic Microorganisms

14.2C: Cooperation Among Microorganisms

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14.2A: Normal Microbiota and Host Relationships

Normal microbiota are the microorganisms that reside in the bodies of all humans.

Learning Objectives

- Explain the relationship between the normal microbiota and the host upon infection of a pathogen

Key Points

- The phrase “normal microbiota ” refers to the microorganisms that reside on the surface and deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts of every human being.
- These microbiota are not harmful to humans; some are even beneficial and most help maintain our health.
- Our normal microbiota consists of various bacteria, fungi, and archaea.
- While our bodies are happy to host the array of microbiota that are considered “normal,” the human body does not take a back seat when infection tries to use it as a host.
- Resistance to and recovery from viral infections depends on the interactions that occur between virus and host. The host has a variety of barriers that it uses to prevent infection. One of the first lines of defense is mucus, which has a range of normal microbiota.
- There are a number of other humoral components of the nonspecific immune system as well.

Key Terms

- **host**: A cell or organism which harbors another organism or biological entity, usually a parasite.
- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **interferon**: Any of a group of glycoproteins, produced by the immune system, that prevent viral replication in infected cells.

Normal Microbiota

The phrase “normal microbiota” refers to the microorganisms that reside on the surface and deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts of every human being. These microorganisms are not harmful to humans; in fact, some are even beneficial and all help maintain our health. Our normal microbiota consists of various bacteria, fungi, and archaea. An example of our bacterial microbiota is *E. coli* . Many people think of *E. coli* as the bacteria that makes you sick; however while it has that capacity, it can also remain dormant and benign in your gastrointestinal tract for your entire life. All humans actually acquire *E. coli*shortly after birth with the intake of food or water. Other forms of bacteria present in the human gut are necessary for proper digestion of carbohydrates.

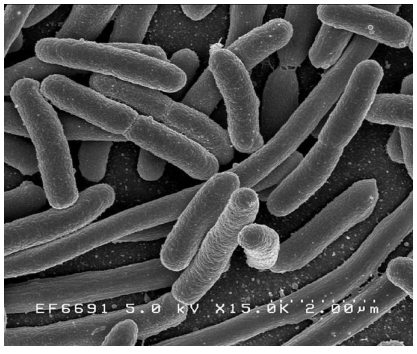

Figure: **Escherichia coli**: This is a magnified view of Escherichia coli (or E. coli).

Host Relationships

While our bodies are happy to host the array of microbiota that are considered “normal,” the human body does not take a back seat when infection tries to use it as a host. Interestingly, normal microbiota can be key players helping the body fight off infection. Resistance to and recovery from viral infections depends on the interactions that occur between the virus and its host. The host has a variety of defenses that it uses to prevent infection. One of the first lines of defense is mucus, which has a range of normal microbiota that compete with and may even attack invading bacteria and virae.

Once a virus or bacteria makes its way past the skin and mucosa, there may be changes that occur in the host to diminish the invader's effectiveness. An example of such a change is a fever. There are a number of other humoral components of the nonspecific immune system as well. Specific immune responses are produced by antibodies. Different interferons (IgA, IgG, IgM, etc.) play roles in defeating viruses located in our membranes. The body does not easily become a host to infection; it has a line up of defenses to try to protect you from harm.

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14.2B: Opportunistic Microorganisms

Learning Objectives

- Describe the traits of an opportunistic microorganism

In the general realm of biology, an opportunist is an organism that is able sustain its life from a number of different sources, but when favorable conditions arise, the organism immediately takes advantage of the opportunity to thrive. When the focus is turned more specifically to microbiology, scientists call organisms that behave this way opportunistic microorganisms. A microorganism is a microscopic organism that can either be a single cell, cell cluster, or multicellular. Microorganisms are very diverse and include bacteria, fungi, algae, and protozoa. Opportunistic microorganisms are typically non-pathogenic microorganisms that act as a pathogen in certain circumstances. They lay dormant for long periods of time until the hosts' immune system is suppressed and then they seize the opportunity to attack.

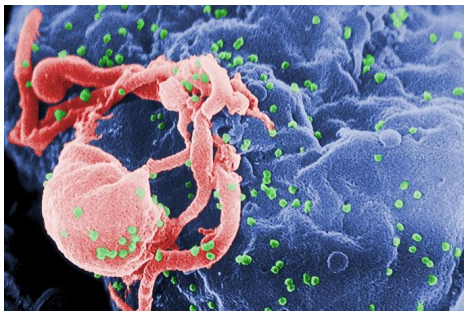

Figure: **HIV**: This is a magnified view of HIV budding from a lymphocyte.

Patients with Human Immunodeficiency Virus (HIV) are particularly susceptible to opportunistic infections. HIV can develop into Acquired Immune Deficiency Syndrome (AIDS), which infects and destroys helper T cells (specifically CD4+ T cells). When the number of CD4+ T cell numbers fall below a critical level, cell-mediated immunity is lost. When immunity is lost, the opportunistic microorganisms can easily infect the AIDS patient without being destroyed by the immune system. These opportunistic pathogens thrive while the human body slowly deteriorates.

An example of an opportunistic microorganism is *Haemophilus ducreyi*. This microorganism infects its host through broken skin or epidermis. In other words, without an open wound, this sexually transmitted disease would be unable to use the human body as a host. It takes advantage of the opportunity to infect the lymphocytes, macrophages and granulocytes as soon as it enters the area of broken skin.

Key Points

- A microorganism is a microscopic organism that can either be a single cell, cell cluster, or multicellular. Microorganisms are very diverse and include bacteria, fungi, algae, and protozoa.
- Opportunistic microorganisms are typically non-pathogenic microorganisms that act as a pathogen in certain circumstances. They lay dormant for long periods of time until the host 's immune system is suppressed and then they take that opportunity to attack.
- Haemophilus ducreyi, a microorganism, infects its host through broken skin or epidermis. Without the open wound, this sexually transmitted disease would be unable to use the human body as a host.

Key Terms

- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **Opportunistic**: Taking advantage of situations that arise.
- **immunodeficiency**: A depletion in the body's natural immune system, or in some component of it.

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14.2C: Cooperation Among Microorganisms

Cooperative behavior, includes mutualism and altruism, benefits one party while the other performs a certain behavior.

Learning Objectives

- Compare and contrast the following cooperative behavior: mutalism and altruism

Key Points

- In microbial systems, there are two main types of cooperation, altruism and mutualism.
- Mutualism is a relationship between microorganisms that is mutually beneficial (+/+). This means that both parties are receiving positive things from their interaction.
- Altruism is a relationship between microorganisms that is beneficial to one party, but harmful to the the (+/-). Scientists believe that the individual that is at a loss performs the action because they believe it will ultimately benefit others whom they share a relationship with (like family).

Key Terms

- **Cooperation**: Association for mutual benefit.
- **mutualism**: A relationship between individuals of different species in which both individuals benefit
- **altruism**: Regard for others, both natural and moral; devotion to the interests of others; brotherly kindness; – opposed to egoism or selfishness.

Microbial Cooperation



Figure: **Methanogenic Bacteria in Termites**: Methanogenic bacteria have a syntrophic relationship with protozoans living in the guts of termites. The protozoans break down cellulose, releasing H2 which is then used in methanogenesis.

A cooperative behavior benefits one party while the other performs a certain behavior or takes a particular action. In microbial systems, there are two main types of cooperation, altruism and mutualism. It is important to remember that microorganisms include bacteria, archaea, fungi, and protists. They are too small to be seen with the naked eye, but they play a huge role in the world as we know it and have a great deal of biological diversity.

Mutualism

Mutualism is a relationship between microorganisms that is mutually beneficial (+/+). This means that both parties benefit from their interaction. A microbial example is the interaction between protozoa and archaea in the digestive tracts of some animals. These animals eat cellulose which is broken down by the protozoa to obtain energy. This process releases hydrogen as a waste

product, which in turn reduces energy production. Specialized archaea convert the hydrogen (which they need) to methane, which allows energy production to increase. Both the protozoa and archaea benefit from this relationship.

Altruism

Altruism is a relationship between microorganisms that is beneficial to one party, but harmful to the the (+/-). Most scientists believe that the individual that is harmed, or at a loss, performs the action because they believe it will ultimately benefit others whom it is close to or share a relationship with (like family). On a microscopic level, this happens with programmed cell death, or apoptosis. Although it does not seem like it would be beneficial for the cell to die, it has been suggested that the resources it was using could be better utilized by other cells for growth and survival.

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SECTION OVERVIEW

14.3: Penetrating Host Defenses

Topic hierarchy

14.3A: Penetrating Host Defenses

14.3B: Pili and Pilus Assembly

14.3C: Biofilms and Infections

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14.3A: Penetrating Host Defenses

Learning Objectives

- Recognize the ways a host can be infected by, and resist, pathogens

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect. Organisms that are expected to be present, and that under normal circumstances do not cause disease, but participate in maintaining health, are deemed members of the normal flora.

Many of the bacteria in the digestive tract, collectively referred to as the gut flora, are able to break down certain nutrients such as carbohydrates that humans otherwise could not digest. The majority of these commensal bacteria are anaerobes, meaning they survive in an environment with no oxygen. Normal flora bacteria can act as opportunistic pathogens at times of lowered immunity. *Escherichia coli* (*E. coli*) is a bacterium that lives in the colon. It is an extensively studied model organism. Certain mutated strains of these gut bacteria do cause disease. An example is *E. coli* O157:H7.

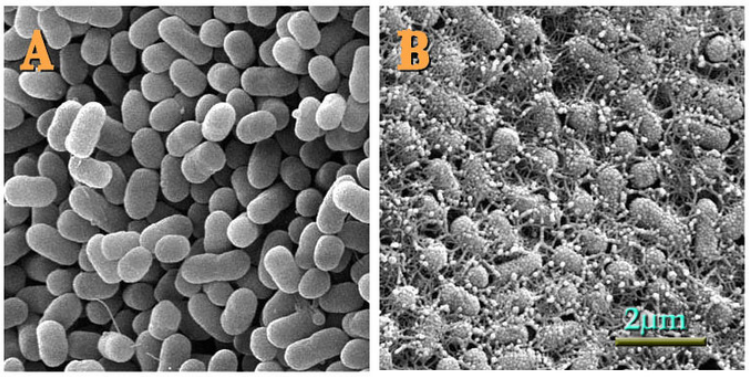

Figure: **Escherichia coli O157:H7**: Topographical images of colonies of *E. coli* O157:H7 strains (A) 43895OW (curli non-producing) and (B) 43895OR (curli producing) grown on agar for 48 h at 28°C. Escherichia coli O157:H7 is an enterohemorrhagic strain of the bacterium Escherichia coli and a cause of food borne illness. Infection often leads to hemorrhagic diarrhea and occasionally to kidney failure, especially in young children and elderly persons. Transmission is via the fecal-oral route. Most illness has been associated with eating under cooked, contaminated ground beef or ground pork, swimming in or drinking contaminated water, or eating contaminated vegetables.

Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication, and the host's reaction to these organisms and the toxins they produce. Infections are caused by pathogens such as viruses, prions, bacteria, and viroids, and larger organisms like macroparasites and fungi.

It is important to keep in mind that although the immune system has evolved to be able to control many pathogens, pathogens themselves have evolved ways to evade the immune response. An example already mentioned is in *Mycobactrium tuberculosis*, which has evolved a complex cell wall that is resistant to the digestive enzymes of the macrophages that ingest them, and thus persists in the host, causing the chronic disease tuberculosis. This section briefly summarizes other ways in which pathogens can "outwit" immune responses. But keep in mind, although it seems as if pathogens have a will of their own, they do not. All of these evasive "strategies" arose strictly by evolution, driven by selection.

Bacteria sometimes evade immune responses because they exist in multiple strains, such as different groups of *Staphylococcus aureus*. *S. aureus* is commonly found in minor skin infections, such as boils, and some healthy people harbor it in their nose. One small group of strains of this bacterium, however, called methicillin-resistant *Staphylococcus aureus*, has become resistant to multiple antibiotics and is essentially untreatable. Different bacterial strains differ in the antigens on their surfaces. The immune response against one strain (antigen) does not affect the other; thus, the species survives.

Another method of immune evasion is mutation. Because viruses' surface molecules mutate continuously, viruses like influenza change enough each year that the flu vaccine for one year may not protect against the flu common to the next. New vaccine formulations must be derived for each flu season.

Genetic recombination—the combining of gene segments from two different pathogens—is an efficient form of immune evasion. For example, the influenza virus contains gene segments that can recombine when two different viruses infect the same cell. Recombination between human and pig influenza viruses led to the 2010 H1N1 swine flu outbreak.

Pathogens can produce immunosuppressive molecules that impair immune function, and there are several different types. Viruses are especially good at evading the immune response in this way, and many types of viruses have been shown to suppress the host immune response in ways much more subtle than the wholesale destruction caused by HIV.

Key Points

- Infections are caused by pathogens such as viruses, prions, bacteria, and viroids, and larger organisms like macroparasites and fungi.
- Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response.
- Pathogens can evade the body's immune responses through means that include specialized adaptations, mutation, evolved resistance to treatments, genetic recombination, and the production of immunosuppressive molecules that impair immune function.

Key Terms

- **Human microbiome**: The aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts.

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14.3B: Pili and Pilus Assembly

Learning Objectives

- Describe the function of the pili in regards to pathogenecity

A pilus (Latin for “hair;” plural: pili) is a hairlike appendage found on the surface of many bacteria. The terms pilus and fimbria (Latin for “thread” or “fiber,” plural: fimbriae) can be used interchangeably, although some researchers reserve the term pilus for the appendage required for bacterial conjugation. All pili are primarily composed of oligomeric pilin proteins.

Dozens of these structures can exist on the bacteria. Some bacterial viruses or bacteriophages attach to receptors on pili at the start of their reproductive cycle. Pili are antigenic. They are also fragile and constantly replaced, sometimes with pili of different composition, resulting in altered antigenicity. Specific host responses to old pili structure are not effective on the new structure. Recombination genes of pili code for variable (V) and constant (C) regions of the pili (similar to immunoglobulin diversity).

Conjugative pili allow the transfer of DNA between bacteria, in the process of bacterial conjugation. They are sometimes called “sex pili”, in analogy to sexual reproduction, because they allow for the exchange of genes via the formation of “mating pairs”. Perhaps the most well-studied is the F pilus of Escherichia coli, encoded by the F plasmid or fertility factor.

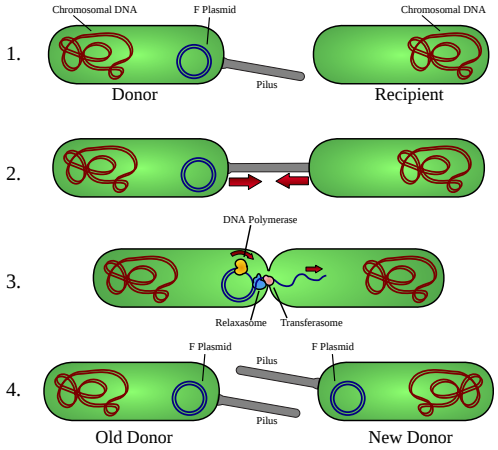

Figure: **Bacterial Conjugation**: A schematic drawing of bacterial conjugation. Conjugation diagram 1- Donor cell produces pilus. 2- Pilus attaches to recipient cell, brings the two cells together. 3- The mobile plasmid is nicked, and a single strand of DNA is then transferred to the recipient cell. 4- Both cells recircularize their plasmids, synthesize second strands, and reproduce pili; both cells are now viable donors.

A pilus is typically 6 to 7 nm in diameter. During conjugation, a pilus emerging from donor bacterium ensnares the recipient bacterium, draws it in close, and eventually triggers the formation of a mating bridge, which establishes direct contact and the formation of a controlled pore that allows transfer of DNA from the donor to the recipient. Typically, the DNA transferred consists of the genes required to make and transfer pili (often encoded on a plasmid), and is a kind of selfish DNA; however, other pieces of DNA often are co-transferred, and this can result in dissemination of genetic traits, such as antibiotic resistance, among a bacterial population. Not all bacteria can make conjugative pili, but conjugation can occur between bacteria of different species.

Some pili, called “type IV pili,” generate motile forces. The external ends of the pili adhere to a solid substrate, either the surface to which the bacteria are attached or to other bacteria, and when the pilus contracts, it pulls the bacteria forward, like a grappling hook. Movement produced by type IV pili is typically jerky, and so it is called “twitching motility,” as distinct from other forms of bacterial motility, such as motility produced by flagella. However, some bacteria, for example Myxococcus xanthus, exhibit gliding motility. Bacterial type IV pilins are similar in structure to the component flagellins of Archaeal flagella.

Attachment of bacteria to host surfaces is required for colonization during infection or to initiate formation of a biofilm. A fimbria is a short pilus that is used to attach the bacterium to a surface. Fimbriae are either located at the poles of a cell or are evenly spread over its entire surface. Mutant bacteria that lack fimbriae cannot adhere to their usual target surfaces and, thus, cannot cause diseases. Some fimbriae can contain lectins. The lectins are necessary to adhere to target cells, because they can recognize oligosaccharide units on the surface of these target cells. Other fimbriae bind to components of the extracellular matrix. Fimbriae are found in both Gram-negative and Gram-positive bacteria. In Gram-positive bacteria, the pilin subunits are covalently linked.

Key Points

- The process of bacterial conjugation allow for the exchange of genes via the formation of “sex pili”.
- All pili are primarily composed of oligomeric pilin proteins.
- Conjugative pili allow the transfer of DNA between bacteria in the process of bacterial conjugation.

Key Terms

- **pilus**: A hair-like appendage found on the cell surface of many bacteria.

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14.3C: Biofilms and Infections

Biofilms will form on virtually every non-shedding surface in a non-sterile aqueous (or very humid) environment.

Learning Objectives

- Discuss the importance of biofilms in the biomedical community

Key Points

- Biofilms have been found to be involved in a wide variety of microbial infections in the body.
- Microbes form a biofilm in response to many factors, which may include cellular recognition of specific or non-specific attachment sites on a surface and nutritional cues.
- Bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds.

Key Terms

- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.
- **sterile**: unable to reproduce (or procreate)

A biofilm is an aggregate of microorganisms in which cells adhere to each other on a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS).

Microbes form a biofilm in response to many factors, which may include cellular recognition of specific or non-specific attachment sites on a surface, nutritional cues, or in some cases, by exposure of planktonic cells to sub-inhibitory concentrations of antibiotics. When a cell switches to the biofilm mode of growth, it undergoes a phenotypic shift in behavior in which large suites of genes are differentially regulated.

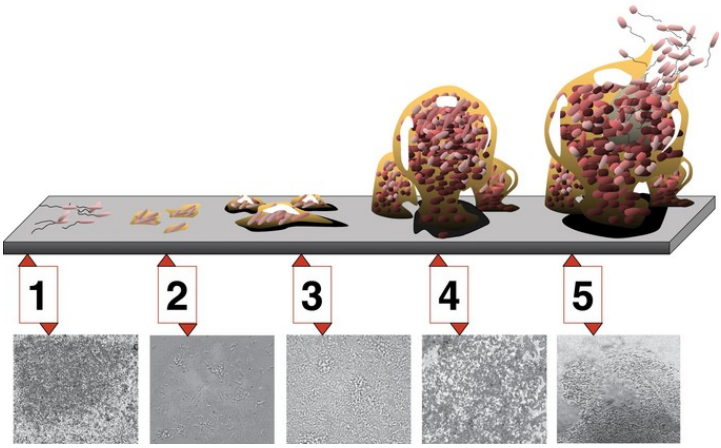

Figure: **Biofilm development**: 5 stages of biofilm development. Stage 1, initial attachment; stage 2, irreversible attachment; stage 3, maturation I; stage 4, maturation II; stage 5, dispersion. Each stage of development in the diagram is paired with a photomicrograph of a developing Pseudomonas aeruginosa biofilm. All photomicrographs are shown to same scale.

Biofilms are ubiquitous. Nearly every species of microorganism, not only bacteria and archaea, have mechanisms by which they can adhere to surfaces and to each other. Biofilms will form on virtually every non-shedding surface in a non-sterile aqueous (or very humid) environment.

Biofilms have been found to be involved in a wide variety of microbial infections in the body, by one estimate in 80% of all infections. Infectious processes in which biofilms have been implicated include common problems such as urinary tract infections, catheter infections, middle-ear infections, formation of dental plaque, gingivitis, and coating contact lenses. Biofilms have also been implicated in less common but more lethal processes such as endocarditis, infections in cystic fibrosis, and infections of permanent indwelling devices such as joint prostheses and heart valves.

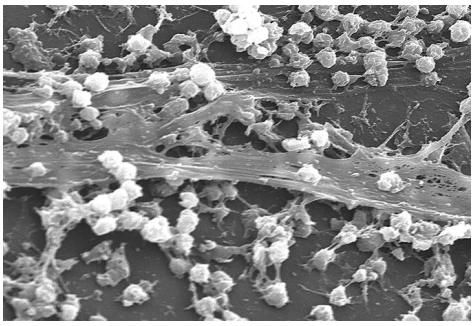

Figure: **Staphylococcus aureus biofilm**: Staphylococcus aureus forming a biofilm on a catheter.

More recently it has been noted that bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds. It has recently been shown that biofilms are present on the removed tissue of 80% of patients undergoing surgery for chronic sinusitis. The patients with biofilms were shown to have been denuded of cilia and goblet cells, unlike the controls without biofilms who had normal cilia and goblet cell morphology. Biofilms were also found on samples from two of 10 healthy controls mentioned. The species of bacteria from interoperative cultures did not correspond to the bacteria species in the biofilm on the respective patient's tissue. In other words, the cultures were negative though the bacteria were present.

Biofilms can also be formed on the inert surfaces of implanted devices such as catheters, prosthetic cardiac valves, and intrauterine devices. New staining techniques are being developed to differentiate bacterial cells growing in living animals, e.g. from tissues with allergy-inflammations.

Pseudomonas aeruginosa biofilms

The achievements of medical care in industrialized societies are markedly impaired due to chronic opportunistic infections that have become increasingly apparent in immunocompromised patients and the aging population. Chronic infections remain a major challenge for the medical profession and are of great economic relevance because traditional antibiotic therapy is usually not sufficient to eradicate these infections.

Pseudomonas aeruginosa is not only an important opportunistic pathogen and causative agent of emerging nosocomial infections but can also be considered a model organism for the study of diverse bacterial mechanisms that contribute to bacterial persistence. In this context the elucidation of the molecular mechanisms responsible for the switch from planktonic growth to a biofilm phenotype and the role of inter-bacterial communication in persistent disease should provide new insights. It should help researchers learn about the pathogenicity of P. aeruginosa, contribute to a better clinical management of chronically infected patients, and lead to the identification of new drug targets for the development of alternative anti-infective treatment strategies.

Dental plaque

Dental plaque is a biofilm that adheres to teeth surfaces and consists of bacterial cells, salivary polymers, and bacterial extracellular products. This accumulation of microorganisms subject the teeth and gingival tissues to high concentrations of bacterial metabolites which results in dental disease. The biofilms attached to the surfaces of some dental alloys, impression materials, dental implants, restorative and cement materials play an essential role concerning the biofilms establishment dynamics toward the physical-chemical properties of the materials which biofilms are attached to.

Legionellosis

Legionella bacteria are known to grow under certain conditions in biofilms, in which they are protected against disinfectants. Workers in cooling towers, persons working in air conditioned rooms, and people taking a shower are exposed to Legionella by inhalation when the systems are not well designed, constructed, or maintained. Neisseria gonorrhoeae is an exclusive human pathogen. Recent studies have demonstrated that it utilizes two distinct mechanisms for entry into human urethral and cervical epithelial cells involving different bacterial surface ligands and host receptors. In addition, it has been demonstrated that the gonococcus can form biofilms on glass surfaces and over human cells. There is evidence for the formation of gonococcal biofilms on human cervical epithelial cells during natural disease. Evidence also suggests that the outer membrane blebbing by the gonococcus is crucial in biofilm formation over human cervical epithelial cells.

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SECTION OVERVIEW

14.4: Damaging Host Cells

Topic hierarchy

14.4A: Toxins

14.4B: Direct Damage

14.4C: Type III and Type IV Secretion

14.4D: Plasmids and Lysogeny

14.4E: Siderophores

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14.4A: Toxins

Learning Objectives

- Describe the major toxin types (bacterial toxins and mycotoxins) and their mechanisms of action

Toxins are poisonous substances produced within living cells or organisms and can include various classes of small molecules or proteins that cause disease on contact. The severity and type of diseases caused by toxins can range from minor effects to deadly effects. The organisms which are capable of producing toxins include bacteria, fungi, algae, and plants. Some of the major types of toxins include, but are not limited to, environmental, marine, and microbial toxins. Microbial toxins may include those produced by the microorganisms bacteria (i.e. bacterial toxins) and fungi (i.e. mycotoxins).

Bacterial Toxins

Bacterial toxins are typically classified under two major categories: exotoxins or endotoxins. Exotoxins are immediately released into the surrounding environment whereas endotoxins are not released until the bacteria is killed by the immune system. The release of toxins into the surrounding environment, regardless of when released, results in the disruption of metabolic pathways in the host eukaryote. These metabolic pathways include damaging cell membranes, disrupting protein synthesis, inhibiting neurotransmitter release, or activating the host immune system. The mechanisms of action by which toxins disrupt eukaryotic cell processes are dependent on the target. For example, the bacteria *Listeria monocytogenes*, associated with food-borne illnesses, specifically targets cholesterol by producing a pore-forming toxin protein, listeriolysin O. This exotoxin affects intracellular processes and creates unregulated pores within the cell membranes of the host. Another example of an exotoxin includes an enterotoxin produced by the bacteria *Staphlycoccal aureus. S. aureus* can producestaphylococcal enterotoxin B (SEB), associated with intestinal illness, which promotes activation of the immune system. Upon activation of the immune system, the release of large amounts of cytokines, inflammatory related molecules, causes significant inflammation. Lastly, an example of an endotoxin, includes the protein lipopolysaccharide (LPS) produced by gram-negative bacteria. The LPS is a component of the bacteria's outer membrane and promotes structural integrity. Upon destruction of the membrane by an immune response, the LPS is released and functions as a toxin.

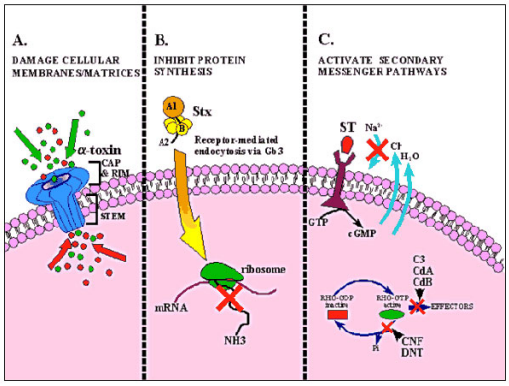

Figure: ***Bacterial Toxin Mechanism of Action****: A schematic of various processes utilized by bacterial toxins to damage host cells.*

However, bacterial toxins are also currently serving as new sources for potential drug development. Toxins have been shown to exhibit anticancer characteristics and fight again microbial virulence. The investigation of toxins as potential medicinal compounds is currently underway.

Mycotoxins

Mycotoxins are the classes of toxins produced by fungi. Mycotoxins are numerous and production of a specific mycotoxin is not restricted to one specific species. Mycotoxins are secondary metabolites that are toxic to humans and produced by fungi. There are various types of mycotoxins including, but not limited to, aflatoxins, ochratoxins, citrinin, and ergot alkaloids.

Aflatoxins

Aflatoxins are a type of mycotoxin that are produced by certain strains of *Aspergillus* fungi. The aflatoxins are further broken down into types: AFB1, AFB2, AFG1, and AFG2. These strains are present in a wide range of agricultural commodities associated with

tropic and subtropic zones. These commodities include species of peanuts and corn. The most potent toxin is AFB1 and it is associated with carcinogenic effects.

Ochratoxin

Ochratoxin is a type of toxin produced by both *Penicillium* and *Aspergillus* species. Ochratoxins are further classified in types A, B and C and differ in structure. Ochratoxins have demonstrated carcinogenic properties and are often found in beverages such as beer and wine, as the fungal species which produce ochratoxins are often found on the plants used to produce these products.

Citrinin

Citrinin is a mycotoxin that has been isolated in numerous species of both *Penicillium* and *Aspergillus*. Many of these fungal species are utilized in food processing and are often found in foods including cheese, wheat, rice, corn, and soy sauce. Citrinin is known to function as a nephrotoxin, indicating it has toxic effects on kidney function.

Ergot Alkaloids

Ergot Alkaloids are specific compounds that are produced as toxic alkaloids in *Claviceps*, a group of fungi associated with grasses, rye, and related plants. The disease caused by ingestion of this fungi is called ergotism. Ergotism is characterized by detrimental effects on the vascular system in particular, including vasoconstriction of blood vessels resulting in gangrene, and eventually, limb loss if left untreated. Additionally, ergotism can present as hallucinations and convulsions as ergot alkaloids target the central nervous system. Due to the vascular system effects of ergot alkaloids, they have been used for medicinal purposes.

Key Points

- Microbial toxins may include those produced by the microorganisms bacteria (i.e. bacterial toxins) and fungi (i.e. mycotoxins).
- Bacterial toxins can include both endotoxins and exotoxins, which vary in mechanism of action and are species -specific.
- Exotoxins are immediately released into the surrounding environment whereas endotoxins are not released until the bacteria is killed by the immune system.
- Mycotoxins can be classified into numerous categories and are not species-specific because the same mycotoxin can be produced by different fungal species.

Key Terms

- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.
- **exotoxin**: Any toxin secreted by a microorganism into the surrounding environment.
- **cytokines**: Regulatory proteins that function in the regulation of the cells involved in immune system function

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14.4B: Direct Damage

Direct damage to the host is a general mechanism utilized by pathogenic organisms to ensure infection and destruction of the host cell.

Learning Objectives

- Describe the different processes used by pathogens to damage the host and ensure infection

Key Points

- Pathogenic organisms must have mechanisms in place to evade attack by the immune system.
- Pathogens can produce enzymes that disrupt normal tissue and allow for further invasion into the tissues.
- Pathogens can produce toxins that interfere with protein function deemed necessary by the host cell for proper maintenance.

Key Terms

- **diphtheria**: A disease of the upper respiratory tract caused by a toxin secreted by Corynebacterium diphtheriae.
- **phagocytosis**: the process by which a cell incorporates foreign particles intracellularly.

Direct damage to the host is a general mechanism utilized by pathogenic organisms to ensure infection and destruction of the host cell. The pathogenic organism typically causes damage due to its own growth process. The promotion of disease is characterized by the ability of a pathogenic organism to enter a host and inflict damage and destruction onto the host cell. The pathogenic organism must exhibit specific characteristics that promote its growth into a host cell including, but not limited to, the ability to invade, colonize, and attach to host cells.

The ability of a pathogen to gain entrance to a host cell is fundamental in the ability of the pathogen to promote and cause disease. The ability to manipulate the process of phagocytosis is a mechanism often utilized by bacteria to ensure they effectively invade a host. Phagocytosis is a process utilized by phagocytes (white blood cells) as a defense mechanism to protect from foreign bodies. The phagocytes engulf invaders and present them to additional factors within the immune system that result in their destruction. However, a successful and destructive pathogen often exhibits the ability to evade phagocytosis.

The mechanism(s) utilized by pathogens to avoid phagocytosis include avoiding both contact and engulfment. Pathogens that exhibit the ability to avoid contact utilize various processes to accomplish this, including: the ability to grow in regions of the body where phagocytes are incapable of reaching; the ability to inhibit the activation of an immune response; inhibiting and interfering with chemotaxis which drives the phagocytes to site of infection; and ‘tricking’ the immune system to identify the bacteria as ‘self. ‘ Additional mechanism(s) by which bacteria can avoid destruction is by avoiding engulfment. This is accomplished by the ability of the bacteria to exhibit produce molecules that interfere with the phagocytes ability to internalize the bacteria. Molecules that interfere with this process include certain types of proteins and sugars that block engulfment.

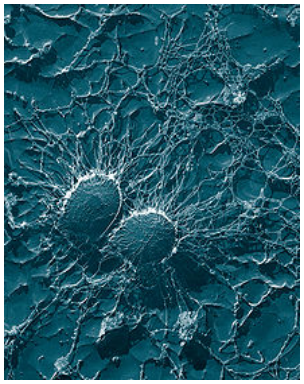

Figure: **Protected from Phagocytosis**: Staphylococcus aureus exhibit physical properties, specifically a capsule, that protect the bacteria from phagocytosis.

Once the pathogen has successfully evaded engulfment and destruction by the immune system, it is detrimental because the bacteria then multiply. Often times, bacteria will directly attach themselves to host cells and utilize nutrients from the host cell for their own cellular processes. Upon the use of host nutrients for its own cellular processes, the bacteria may also produce toxins or enzymes that will infiltrate and destroy the host cell. The production of these destructive products results in the direct damage of

the host cell. The waste products of the microbes will also damage to the cell. Examples of bacteria that will damage tissue by producing toxins, include, *Corynebacterium diphtheriae* and *Streptococcus pyogenes*. Specifically, *Corynebacterium diphtheriae* causes diphtheria, which isa disease of the upper respiratory tract. It produces a toxin, diphtheria toxin, which alters host protein function. The toxin can then result in damage to additional tissues including the heart, liver, and nerves. *Streptococcus pyogenes* is associated with strep throat and “flesh-eating disease. ” The bacteria produce enzymes which function in disrupting fibrin clots. Fibrin clots will form at sites of injury, in this case, at the site of foreign invasion. The enzymes, capable of digesting fibrin, will open an area within the epithelial cells and promote invasion of the bacteria into the tissues.

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14.4C: Type III and Type IV Secretion

Type III and IV secretion systems are utilized by pathogenic bacteria to transfer molecules from the bacterial cell to the host cell.

Learning Objectives

- Distinguish between Type III and IV secretion systems

Key Points

- Type III secretion system use a process which injects the secretory molecule into the host cell.
- Type IV secretion systems use a process which is similar to the bacterial conjugation machinery.
- Type IV secretion systems require attachment to the host cell by direct cell-to-cell contact or via a bridge-like apparatus.
- Type IV secretion systems can be used to both transport and receive molecules.
- Type III secretion systems requires a large protein complex to ensure proper transfer of secretory molecules.

Key Terms

- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.
- **effector**: a small molecule that effects additional molecules
- **bacterial conjugation**: transfer of genetic material between bacterial cells by direct contact

In regards to pathogenecity, secretion in microorganisms such as bacterial species involves the movement of effector molecules from the interior of a pathogenic organism to the exterior. The secretion of specific molecules allows for adaptation to occur, thereby promoting survival. Effector molecules secreted include proteins, enzymes or toxins. The mechanisms by which pathogenic bacteria secrete proteins involve complex and specialized secretion systems. Specifically, Type III and Type IV secretion systems are utilized by gram-negative pathogenic bacteria to transport proteins that function as pathogenic components.

Type III Secretion Systems

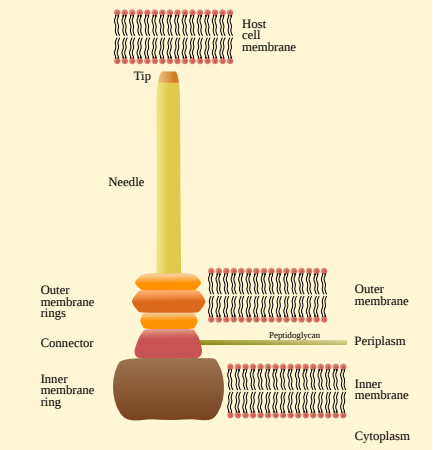

Figure: **Type III Secretion System**: The type III secretion system is characterized by the ability to inject secretory molecules into the host eukaryotic cell.

Type III secretion systems are characterized by the ability to inject a protein directly from the bacterial cell to the eukaryotic cell. It is often compared to the bacterial flagellar basal body which functions as a motor unit and extracellular appendage that is comprised of numerous proteins. The pathogenic bacteria which exhibit this capability contain a critical structural component, considered a protein appendage, that allows the injection of the protein into the host cell. The type III secretion system involves the formation of a complex, roughly ~20 proteins, that reside within the cytoplasmic membrane of the bacterial cell. The process of injecting or transferring the secretory protein from the bacterial cell to the host eukaryotic cell requires a membrane-associated ATPase. Certain species of pathogenic bacteria, including: *Salmonella*, *Shigella*, *Yersinia* and *Vibrio* exhibit type III secretion systems. The system is regulated by Ca2+ concentrations which regulate the opening and closing of gates present in the membrane by which the type III secretion system complexes can utilize for translocation. For example, in *Salmonella*, most commonly associated with *Enteritis salmonellosis*, or food poisoning, the bacteria injects a toxin, AvrA, that inhibits activation of the innate immune system of the host. The mechanism by which AvrA is injected involves exact and proper assembly of proteins which

promote invasion of the host cell. Misalignment or improper organization of proteins involved in the type III secretion system prevent injection of secretory substances from the pathogen into the host cell. Another pathogen, *Shigella*, which utilizes type III secretion systems is able to successfully carry out its infection by evading the immune system. The movement between neighboring cells and evading the immune system, enhances its ability to inject its secretory protein into the host cell.

Type IV Secretion Systems

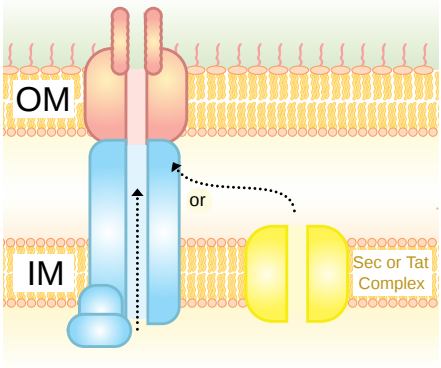

Figure: **Type IV Secretion System**: Type IV secretion systems are characterized by the ability to transfer material using machinery similar to the bacterial conjugation machinery.

Type IV secretion systems are characterized by the ability to transfer secretory molecules via a mechanism similar to the bacterial conjugation machinery. The type IV secretion systems can either secrete or receive molecules. The bacterial conjugation machinery allows transfer of genetic material to occur via direct cell-to-cell contact or by a bridge-like apparatus between the two cells. The type IV secretion system utilizes a process similar to this. However, the exact mechanism(s) this process utilizes is unknown but there is a general understanding.

This specific secretion system can transport both DNA and proteins. An example of a pathogenic bacteria that utilizes the type IV secretion system is *Helicobacter pylori*. *H. pylori*, most commonly associated with stomach ulcers, attaches itself to epithelial cells within the stomach, then via a type IV secretion system, injects a secretory molecule. The secretory molecule injected into the epithelial cells is an inflammation-inducing agent derived from their own cellular wall. The secretory molecule, peptidoglycan, is recognized by the host system as a foreign substance and activates expression of cytokines which promotes an inflammatory response. This inflammatory response of the stomach is a key characteristic of individuals with ulcers. Peptidoglycan is not the only secretory molecule transferred to the stomach epithelial cells but additional proteins, such as CagA, which function in disruption of host cell cellular activities can be transferred as well.

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14.4D: Plasmids and Lysogeny

Learning Objectives

- Distinguish between plasmids and lysogeny in regards to pathogenecity

Plasmids

Plasmids are DNA molecules that are capable of replicating independently from the chromosomal DNA. Plasmids are often characterized by their circular appearance and double-strands; they also vary in size and number. Plasmids are present in the three major domains (Archaea, Bacteria and Eukarya) and are considered to be 'naked DNA'. 'Naked DNA' refers to a specific type of DNA which does not encode for genes promoting the transfer of genetic material to a new host. The plasmids are present within the cells as extra chromosomal genomes and are a common tool used in molecular biology to integrate new DNA into a host. In the field of molecular biology, plasmid DNA is often referred to as ' vectors ' due to their ability to transfer DNA between organisms. The use of plasmid DNA in molecular biology is considered to be recombinant DNA technology. In addition, plasmid DNA provides a mechanism by which horizontal gene transfer can occur, contributing to antibiotic resistance.

Horizontal gene transfer is a major mechanism promoting bacterial antibiotic resistance, as the plasmid DNA can transfer genes from one species of bacteria to another. The plasmid DNA which is transferred often has developed genes that encode for resistance against antibiotics. The ability to transfer this resistance from one species to another is increasingly becoming an issue in clinics for treatment of bacterial infections. The process of horizontal gene transfer can occur via three mechanisms: transformation, transduction and conjugation. Plasmid DNA transfer is associated with conjugation as the host-to-host transfer requires direct mechanical transfer. The advantages of plasmid DNA transfer allow for survival advantages.

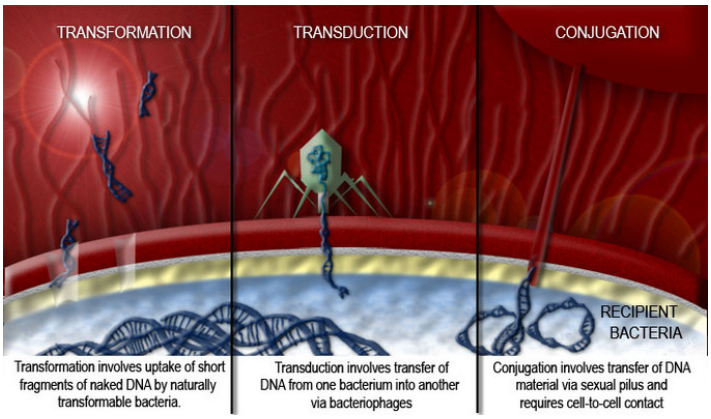

Figure: **Horizontal Gene Transfer**: There are three mechanisms by which horizontal gene transfer can occur. Specifically, the exchange of plasmid DNA falls under transformation.

Lysogeny

Lysogeny is the process by which a bacteriophageintegrates its nucleic acids into a host bacterium's genome. Lysogeny is utilized by viruses to ensure the maintenance of viral nucleic acids within the genome of the bacterium host. The virus displays the ability to infect the bacterium host and integrate its own genetic materials into the host bacterium genome. The bacteriophages newly integrated genetic material, called a prophage, is transferred to new bacterial daughter cells upon cell division. The prophage is integrated into the bacterium genome at this point. The lysogenic cycle is key to ensure the transmittance of bacteriophage nucleic acids to host bacterium's genome. Lysogeny is one of two major methods of viral reproduction utilized by viruses.

Lysogenic cycles are utilized by specific types of viruses to ensure viral reproduction, but they also need the second major method of viral reproduction, the lytic cycle, as well. The lytic cycle, considered the primary method of viral replication, results in the actual destruction of the infected cell. Upon destruction of the infected cell, the new viruses, which have developed after undergoing biosynthesis and maturation, are free to infect other cells. The lytic cycle is characterized by the breakdown of the bacteria cell wall intracellularly. The viruses cause disruption of the bacterial cell by producing enzymes which facilitate this process. An example of a virus which can promote the transformation of bacterium from a nontoxic to toxic strain via lysogeny is the CTXφ virus. Specifically, the bacterium, *Vibrio cholerae*, is transformed into a toxic strain upon infection with the bacteriophage. This bacterium is then able to produce a cholera toxin, the cause of the disease cholera.

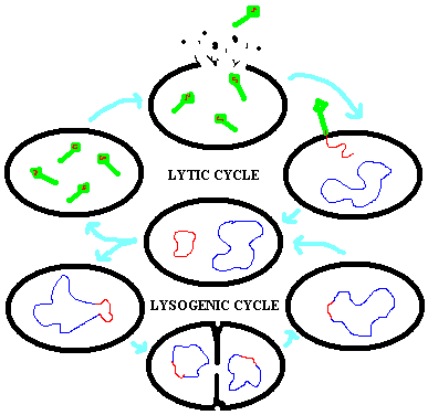

Figure: ***Lysogenic and lytic cycles****: Schematic of lysogenic and lytic cycle utilized by viruses to ensure viral reproduction.*

Key Points

- Plasmids are double-stranded circular forms of ‘naked DNA ‘.
- Plasmids are responsible for horizontal gene transfer which promotes the development of antibiotic resistance in bacterium.
- Lysogeny is a major method of viral reproduction characterized by the integration of viral nucleic acids in the bacterium genome.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.
- **lysogeny**: the process by which a bacteriophage incorporates its nucleic acids into a host bacterium

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14.4E: Siderophores

Learning Objectives

- Compare and contrast the role of various siderophores in pathogenecity, including: yersiniabactin, enterobactin and ferrichromes

Siderophores are specific types of molecules utilized by microorganisms to obtain iron from the environment. Specifically, in regards to pathogenicity, organisms that exhibit the ability to produce siderophores release these iron-specific molecules and scavenge iron from their hosts organisms. The siderophores are then utilized by the pathogen to obtain iron. Therefore, siderophores are chelating agents that bind the iron ions. The ability of pathogens to obtain iron from the host is essential for survival because the iron is limited in the host environment, in particular, the host tissues and fluids. The iron is used to allow for formation of soluble ferric ion (Fe^{3+}) complexes that are necessary for maintenance of homeostatic mechanisms within the pathogen.

The ability to form water soluble Fe^{3+} complexes is a key component to the active transport of the Fe-siderophore complex across the cellular membrane. In iron deficient environments, the siderophores are released and allow for the formation of water soluble-Fe^{3+} complexes to increase iron acquisition. The complexes then generally bind to the cellular membrane using cell specific receptors. They are transported across the membrane utilized for the necessary processes. However, there are differences in the mechanisms employed by various sideorophobes to obtain iron and the specific type of siderophore utilized varies.

Yersiniabactin

The pathogenic bacteria, *Yersinia pestis*, *Yersinia pseduotuberculosis*, and *Yersinia enterocolitica* have the ability to produce a siderophore called yersiniabactin. Pathogenic yersinia is responsible for numerous diseases including the bubonic plague. The ability of pathogenic Yersinia to establish and spread disease is based on its ability to obtain iron for fundamental cellular processes. In areas of low iron, the organism will release yersiniabactin to form Fe^{3+} complexes. The yersiniabactin-Fe^{3+} complex will then bind to the outer membrane of the bacteria based on specific receptor recognition. The complex is then translocated through the membrane via membrane-embedded proteins and iron is released from the yersiniabactin. The iron will then be utilized in numerous cellular processes.

Enterobactin

Pathogenic bacteria such as *Escherichia coli* and *Salmonella typhimurium* have the ability to produce a siderophore called enterobactin. This specific type of siderophore is the strongest identified siderophore, to date, with an extremely high binding affinity to Fe^{3+}. Upon a decrease in iron, the bacterial cells release enterobactin which forms a complex with Fe^{3+}. The complex is then transported intracellularly via an ATP-binding cassette transporter. Once the enterobactin-Fe^{3+} complex arrives intracellularly, it is necessary to remove the Fe^{3+} from the complex. Due to the high-binding affinity of enterobactin, the bacteria require a highly specific enzyme, ferrienterobactin esterase, to cleave the iron from the complex. The iron released from the complex will then be utilized in metabolic processes.

Ferrichrome

Another type of siderophore produced by pathogenic fungi includes a ferrichrome. Fungi that have been shown to produce ferrichromes include those in the genera Aspergillus, Ustilago, and Penicillum. The ferrichrome allows for formation of a ferrichrome-iron complex which can then interact with a protein receptor on the cell surface. The ferrichrome promotes iron transport within the organism to allow metabolic processes to occur.

The discovery and identification of siderophores have allowed for the development of treatments targeting these siderophore-iron complexes. By targeting these complexes, the pathogenic microorganisms can be targeted by inhibiting necessary cellular processes. The production and importance of these siderophores to pathogenic organisms is key to their survival.

Key Points

- Siderophore – iron complexes are necessary for iron acquisition to various pathogenic organisms for metabolic processes.
- The types of siderophores produced are species specific and exhibit different properties.

- The siderophores are necessary to obtain iron by binding to cell surfaces and transporting the siderophore-iron complexes intracellularly.
- Siderophores are produced in environments that have low iron concentration, such as host tissues and fluids. They are considered advantageous to pathogenic organisms.

Key Terms

- **siderophore**: Any medium-sized molecule that has a high specificity for binding or chelating iron; they are employed by microorganisms to obtain iron from the environment
- **chelating agent**: A compound that reacts with a metal ion to produce a chelate.

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SECTION OVERVIEW

14.5: Surviving Within the Host and Exiting the Host

Topic hierarchy

14.5A: Intracellular Pathogens

14.5B: Extracellular Immune Avoidance

14.5C: Regulating Virulence

14.5D: Portals of Exit

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14.5A: Intracellular Pathogens

Learning Objectives

- Recognize examples of intracellular pathogens

A pathogen or infectious agent is a microorganism such as a virus, bacterium, prion, or fungus that causes disease in its host. The host may be an animal, a plant, or even another microorganism. Not all pathogens are undesirable to humans. In entomology, pathogens are one of the "Three P's" (predators, pathogens, and parasitoids) that serve as natural or introduced biological controls to suppress arthropod pest populations.

There are several types of intracellular pathogens. Pathogenic viruses are mainly those of the families of Adenoviridae, bacteria Picornaviridae, Herpesviridae, Hepadnaviridae, Flaviviridae, Retroviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Polyomavirus, Rhabdoviridae, and Togaviridae. Viruses typically range between 20 to 300 nanometers in length. Although the vast majority of bacteria are harmless or beneficial, a few pathogenic bacteria can cause infectious diseases. Bacteria can often be killed by antibiotics because the cell wall in the outside is destroyed, expelling the DNA out of the body of the pathogen, therefore making the pathogen incapable of producing proteins, so it dies. They typically range between 1 and 5 micrometers in length.



Figure: ***Stanley Prusiner****: Stanley Prusiner discovered prions, which are a class of infectious self-reproducing pathogens primarily or solely composed of protein.*

Pathogenic fungi comprise a eukaryotic kingdom of microbes that are usually saprophytes but can cause diseases in humans, animals, and plants. Fungi are the most common cause of diseases in crops and other plants. The typical fungal spore size is 1 to 40 micrometers in length.

Some eukaryotic organisms, such as protists and helminths, cause disease. According to the prion theory, prions are infectious pathogens that do not contain nucleic acids. These abnormally-folded proteins are found characteristically in some diseases such as scrapie, bovine spongiform encephalopathy (mad cow disease), and Creutzfeldt–Jakob disease. Although prions fail to meet the requirements laid out by Koch's postulates, the hypothesis of prions as a new class of pathogen led Stanley B. Prusiner to receive the Nobel Prize in Physiology or Medicine in 1997.

Key Points

- The host may be an animal, a plant, or even another microorganism.
- Pathogenic viruses are mainly those of the families of Adenoviridae, bacteria Picornaviridae, Herpesviridae, Hepadnaviridae, Flaviviridae, Retroviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Polyomavirus, Rhabdoviridae, and Togaviridae.
- Although the vast majority of bacteria are harmless or beneficial, a few pathogenic bacteria can cause infectious diseases.

Key Terms

- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.

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14.5B: Extracellular Immune Avoidance

A pathogen's success depends on its ability to evade the host's immune responses.

Learning Objectives

- List the mechanisms that bacteria use for intracellular pathogenesis

Key Points

- Bacteria usually overcome physical barriers by secreting enzymes to digest the barrier in the manner of a type II secretion system.
- Some pathogens avoid the immune system by hiding within the cells of the host, a process referred to as intracellular pathogenesis.
- Other pathogens invade the body by changing the non-essential epitopes on their surface rapidly, while keeping the essential epitopes hidden.

Key Terms

- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.
- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.
- **antigenic variation**: The mechanism by which an infectious organism changes its surface proteins in favor of circumventing a host immune response.

Extracellular Immune Avoidance

A pathogen's success depends on its ability to evade the host's immune responses. Thus, pathogens have evolved several methods that allow them to successfully infect a host by evading the immune system's detection and destruction. Bacteria usually overcome physical barriers by secreting enzymes that digest the barrier in the manner of a type II secretion system. They also use a type III secretion system that allows bacteria to insert a hallow tube, which provides proteins a direct route to enter the host cell. These proteins often shutdown the defenses of the host.

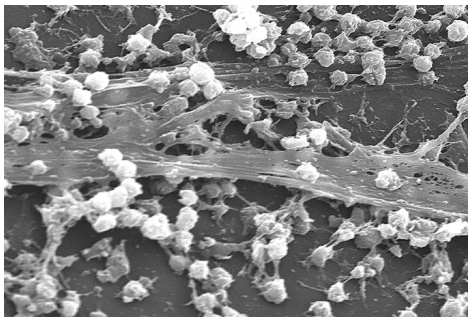

Figure: **Staphylococcus aureus biofilm**: Staphylococcus aureus forming a biofilm on a catheter.

Some pathogens avoid the immune system by hiding within the cells of the host, a process referred to as intracellular pathogenesis. The pathogen hides inside the host cell where it is protected from direct contact with the complement, antibodies, and immune cells. A lot of pathogens release compounds that misdirect or diminish the host's immune response. Some bacteria even form biofilms which protect them from the proteins and cells of the immune system. Many successful infections often involve biofilms. Some bacteria create surface proteins, such as Streptococcus, that will bind to antibodies making them ineffective.

Other pathogens invade the body by changing the non-essential epitopes on their surface rapidly while keeping the essential epitopes hidden. This is referred to as antigenic variation. HIV rapidly mutates so the proteins that are on its viral envelope, which are essential for its entry into the host's target cell, are consistently changing. The constant change of these antigens is why vaccines have not been created. Another common strategy that is used is to mask antigens with host molecules in order to evade detection by the immune system. With HIV, the envelope covering the viron is created from the host cell's outermost membrane making it difficult for the immune system to identify as a non-self structure.

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14.5C: Regulating Virulence

Virulence regulation is a combination of the specific traits of the pathogen and the evolutionary pressures that lead to virulent traits.

Learning Objectives

- Compare and contrast the hypotheses that explain why a pathogen evolves as it does: Trade-Off, Short-Sighted Evolution and Coincidental Evolution Hypotheses

Key Points

- Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host.
- The ability of a microorganism to cause disease is described in terms of the number of infecting bacteria, the route of entry into the body, the effects of host defense mechanisms, and intrinsic characteristics of the microorganism called virulence factors.
- Optimal virulence increases with horizontal transmission (between non-relatives) and decreases with vertical transmission (from parent to child).
- The pathogen population can evolve once it is in the host.
- The three main hypotheses about why a pathogen evolves as it does are the Trade-Off Hypothesis, the Short-Sighted Evolution Hypothesis, and the Coincidental Evolution Hypothesis.

Key Terms

- **virulence**: The degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host and it is determined by virulence factors.

Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism – its ability to cause disease – is determined by its virulence factors. In an ecological context, virulence can be defined as the host's parasite-induced loss of fitness. Virulence can be understood in terms of proximate causes—those specific traits of the pathogen that help make the host ill—and ultimate causes—the evolutionary pressures that lead to virulent traits occurring in a pathogen strain.

The ability of a microorganism to cause disease is described in terms of the number of infecting bacteria, the route of entry into the body, the effects of host defense mechanisms, and intrinsic characteristics of the microorganism called virulence factors. Host-mediated pathogenesis is often important because the host can respond aggressively to infection with the result that host defense mechanisms do damage to host tissues while the infection is being countered.

According to evolutionary medicine, optimal virulence increases with horizontal transmission (between non-relatives) and decreases with vertical transmission (from parent to child). This is because the fitness of the host is bound to the fitness in vertical transmission but is not so bound in horizontal transmission.The pathogen population can evolve once it is in the host. There are three main hypotheses about why a pathogen evolves as it does. These three models help to explain the life history strategies of parasites, including reproduction, migration within the host, virulence, etc.

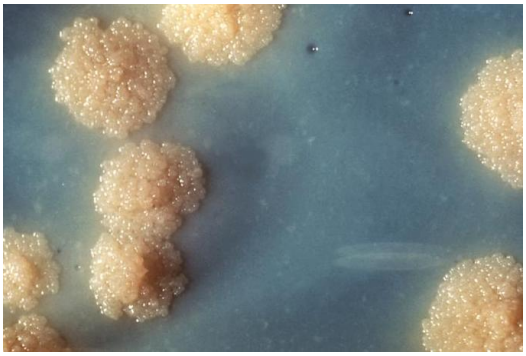

Figure: **Tuberculosis Culture**: The bacteria Mycobacterium tuberculosis can evolve to subvert the protection offered by immune defenses. This close-up reveals this organism's colonial morphology. Note the colorless rough surface, which are typical morphologic characteristics seen in Mycobacterium tuberculosis colonial growth. Macroscopic examination of colonial growth patterns is still one of the ways microorganisms are often identified.

1. Trade-off hypothesis argues that pathogens tend to evolve toward ever decreasing virulence because the death of the host (or even serious disability) is ultimately harmful to the pathogen living inside. For example, if the host dies, the pathogen population inside may die out entirely. Therefore, it was believed that less virulent pathogens that allowed the host to move around and interact with other hosts should have greater success reproducing and dispersing. But this is not necessarily the case. Pathogen strains that kill the host can increase in frequency as long as the pathogen can transmit itself to a new host, whether before or after the host dies. The evolution of virulence in pathogens is a balance between the costs and benefits of virulence to the pathogen.
2. Short-sighted evolution hypothesis suggests that the traits that increase reproduction rate and transmission to a new host will rise to high frequency within the pathogen population. These traits include the ability to reproduce sooner, reproduce faster, reproduce in higher numbers, live longer, survive against antibodies, or survive in parts of the body the pathogen does not normally infiltrate. These traits typically arise due to mutations, which occur more frequently in pathogen populations than in host populations, due to the pathogens' rapid generation time and immense numbers. After only a few generations, the mutations that enhance rapid reproduction or dispersal will increase in frequency. The same mutations that enhance the reproduction and dispersal of the pathogen also enhance its virulence in the host, causing much harm (disease and death). If the pathogen's virulence kills the host and interferes with its own transmission to a new host, virulence will be selected against. But as long as transmission continues despite the virulence, virulent pathogens will have the advantage.
3. Coincidental evolution hypothesis argues that some forms of pathogenic virulence did not co-evolve with the host. For example, tetanus is caused by the soil bacterium Clostridium tetani. After C. tetani bacteria enter a human wound, the bacteria may grow and divide rapidly, even though the human body is not their normal habitat. While dividing, C. tetani produce a neurotoxin that is lethal to humans. But it is selection in the bacterium's normal life cycle in the soil that leads it to produce this toxin, not any evolution with a human host. The bacterium finds itself inside a human instead of in the soil by mere happenstance. We can say that the neurotoxin is not directed at the human host.

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14.5D: Portals of Exit

Pathogens must have a way to be transmitted from one host to another to ensure their species' survival.

Learning Objectives

- Distinguish between horizontal and vertical disease transmission

Key Points

- Transmission of microorganisms can happen directly from one person to another by: droplet contact, direct physical contact, indirect physical contact, airborne transmission, or fecal-oral transmission.
- Transmission can also be indirect, via another organism, either a vector or an intermediate host.
- Disease can also be transmitted in two ways: horizontally from one individual to another in the same generation and vertically from parent to offspring, such as through perinatal transmission.

Key Terms

- **transmission**: Transmission is the passing of a communicable disease from an infected host individual or group to a conspecific individual or group, regardless of whether the other individual was previously infected.

Transmission is the passing of a communicable disease from an infected host individual or group to a conspecific individual or group by one or more of the following means: droplet contact, direct physical contact, indirect physical contact, airborne transmission, and fecal-oral transmission.

Transmission can also be indirect, via another organism. Indirect transmission could involve zoonoses or, more typically, larger pathogens like macroparasites with more complex life cycles. Disease can be directly transmitted in two ways. The first is horizontal disease transmission – from one individual to another in the same generation by either direct contact, or indirect contact air, such as via a cough or sneeze. The second is vertical disease transmission – passing a disease causing agent vertically from parent to offspring, such as through perinatal transmission.

Pathogens must have a way to be transmitted from one host to another to ensure their species ' survival. Infectious agents are generally specialized for a particular method of transmission. For example, a virus or bacteria that causes its host to develop coughing and sneezing symptoms has a great survival advantage – it is much more likely to be ejected from one host and carried to another. This is also the reason that many microorganisms cause diarrhea.

The respiratory route is a typical mode of transmission among many infectious agents. If an infected person coughs or sneezes on another person, the microorganisms, suspended in warm, moist droplets, may enter the body through the nose, mouth, or eye surfaces. Diseases that are commonly spread by coughing or sneezing include: bacterial meningitis and chickenpox.



Figure: **Sneezing**: Sneezing can spread disease by launching disease vectors into the air.

When viruses are shed by an infected person through coughing or sneezing into the air, the mucus coating on the virus starts to evaporate. Once this mucus shell evaporates the remaining viron is called a droplet nucleus or quanta. The mucus evaporation rate is determined by the temperature and humidity inside the room. The lower the humidity, the quicker the mucus shell evaporates thus allowing the droplet nuclei to stay airborne and not drop to the ground. The low indoor humidity levels in wintertime buildings ensure that higher levels of droplet nuclei will survive: droplet nuclei are so microscopic that they are able to stay airborne indefinitely on the air currents present within indoor spaces. When an infected person coughs or sneezes, a percentage of their

viruses will become droplet nuclei. If these droplet nuclei gain access to the eyes, nose, or mouth of an uninfected person (known as a susceptible) – either directly, or indirectly by touching a contaminated surface – then the droplet nuclei may penetrate into the deep recesses of their lungs. Viral diseases that are commonly spread by coughing or sneezing droplet nuclei include the common cold and influenza.

Direct fecal-oral transmission is rare for humans at least. More common are the indirect routes: foodstuffs or water become contaminated and the people who eat and drink them become infected. This is the typical mode of transmission for infectious agents such as cholera, hepatitis A, and polio.

Sexual transmission refers to any disease that can be caught during sexual activity with another person, including vaginal or anal sex or (less commonly) through oral sex. Transmission is either directly between surfaces in contact during intercourse or from secretions which carry infectious agents that get into the partner's blood stream through tiny tears in the penis, vagina, or rectum. Some diseases transmissible by the sexual route include: HIV/AIDS and chlamydia.

Sexually transmitted diseases such as HIV and Hepatitis B are thought to not normally be transmitted through mouth-to-mouth contact, although it is possible to transmit some STDs between the genitals and the mouth during oral sex. In the case of HIV this possibility has been established. It is also responsible for the increased incidence of herpes simplex virus 1 (which is usually responsible for oral infections) in genital infections and the increased incidence of the type 2 virus (more common genitally) in oral infections.

Diseases that can be transmitted by direct contact are called contagious. These diseases can also be transmitted by sharing a towel (where the towel is rubbed vigorously on both bodies) or items of clothing in close contact with the body (socks, for example) if they are not washed thoroughly between uses.

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SECTION OVERVIEW

14.6: Pathogenicity and Other Microbes

Topic hierarchy

14.6A: Fungi

14.6B: Protozoa

14.6C: Helminths

14.6D: Algae

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14.6A: Fungi

A fungus is a member of a large group of eukaryotic organisms that includes microorganisms that exhibit pathogenicity.

Learning Objectives

- Give examples of pathogenic fungi

Key Points

- There are various examples of pathogenic fungi including but not limited too: Candida species, Aspergillosis, Cryptococcus, Histoplasma, Pneumocystis and Stachybotrys.
- Many fungal species produce bioactive compounds called mycotoxins, such as alkaloids and polyketides that are toxic to animals including humans, contributing to pathogenecity and disease.
- The study of pathogenic fungi is referred to as a medical mycology.

Key Terms

- **symbiont**: An organism that lives in a symbiotic relationship; a symbiote.
- **mycotoxin**: Any substance produced by a mold or fungus that is injurious to vertebrates upon ingestion, inhalation, or skin contact.
- **opportunist**: when an organism takes advantage of any opportunity to advance its own situation.

A fungus is a member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds. These organisms are classified as kingdom Fungi, separate from plants, animals, and bacteria. Fungi have a worldwide distribution and cangrow in a wide range of habitats, including extreme environments such as deserts or areas with high salt concentrations or ionizing radiation, as well as in deep sea sediments. Most fungi are inconspicuous because of the small size of their structures and their cryptic lifestyles in soil, on dead matter, and as symbionts of plants, animals, or other fungi. Fungi perform an essential role in the decomposition of organic matter and have fundamental roles in nutrient cycling and exchange. Many fungal species produce bioactive compounds called mycotoxins, such as alkaloids and polyketides that are toxic to animals including humans, contributing to pathogenecity and disease.

The study of pathogenic fungi is referred to as a medical mycology. There are various examples of pathogenic fungi including but not limited too: Candida species, Aspergillosis, Cryptococcus, Histoplasma, Pneumocystis and Stachybotrys.

Candida species are commonly known to cause opportunist infections in immunocompromised hosts. The immunocompromised hosts that commonly become infected with Candida include transplant patients, cancer patients and AIDS sufferers. Candida infections are difficult to treat and can result in systemic infections leading to death.

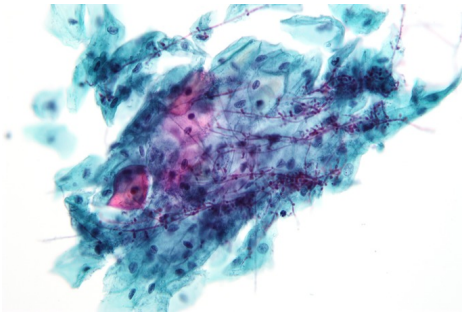

Figure: **Candida**: A Candida infection seen from a pap test specimen.

One of the most commons fungal pathogenic species includes Aspergillus strains, specifically Aspergillus fumigatus and Aspergillus flavus. Aspergillus can cause disease via production of mycotoxins, induction of allergic responses and through localized or systemic infections. Aspergillus flavus specifically produces aflatoxin which is both a toxin and carcinogen whereas Aspergillus fumigatus causes allergic disease. Symptoms of diseases caused by Aspergillus can include fever, cough, chest pain or breathlessness.

Cryptococcus neoformans causes severe forms of meningitis and meningo-encephalitis in patients with HIV infection and AIDS. Cryptococcus species live in the soil and do not cause disease in humans thus, Cryptococcus neoformans is the major pathogen in

both human and animals.

Histoplasma capsulatum results in the formation of histoplasmosis in humans, dogs and cats. This specific fungus is endemic in certain areas of the United States and infection is due to inhaling contaminated air.

Pneumocystis jirovecii results in the formation of pneumonia in individuals with weakened immune systems including premature children, the elderly and AIDS patients.

Stachybotrys chartarum, also referred to as black mold, causes respiratory damage and severe headaches. This type of black mold frequently occurs in households that are chronically damp.

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14.6B: Protozoa

Protozoa are a diverse group of unicellular eukaryotic organisms, many of which can cause disease.

Learning Objectives

- Compare and contrast the proliferative and dormant stages in pathogenic protozoa and the diseases protazoa cause

Key Points

- Examples of human diseases caused by protozoa are: malaria, amoebiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, Chagas disease, leishmaniasis, and dysentery.
- The life stages of these protozoa play a major role in their ability to function as pathogens and infect various hosts.
- Protozoa were regarded as the partner-group of protists to protophyta, which have plant-like behavior (e.g., photosynthesis). In general, protozoa are referred to as animal-like protists because they are capable of movement, or motile.
- Some protozoa are human parasites, causing diseases.

Key Terms

- **trophozoite**: A protozoan in the feeding stage of its life cycle.
- **protozoa**: Protozoa are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior, e.g., movement. Protozoa were regarded as the partner group of protists to protophyta, which have plant-like behavior, e.g., photosynthesis.
- **dormant cyst**: A resting or dormant stage of a microorganism
- **cyst**: a pouch or sac without opening, usually membranous and containing morbid matter, which develops in one of the natural cavities or in the substance of an organ

Protozoa (or protozoans) are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior (e.g., movement). Protozoa were regarded as the partner-group of protists to protophyta, which have plant-like behavior (e.g., photosynthesis). In general, protozoa are referred to as animal-like protists because they are capable of movement, or *motile*. While there is no exact definition for the term protozoa, it often refers to a unicellular heterotrophic protist, such as the amoebas and ciliates.

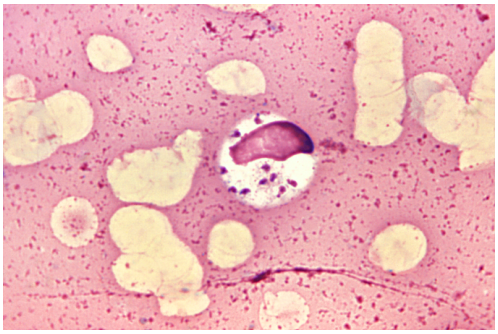

Figure: **Leishmania donovani**: Leishmania donovani, (a species of protozoa) in a bone marrow cell.

Protozoa can display pathogenicity and are the cause of various diseases. The life stages of these protozoa play a major role in their ability to function as pathogens and infect various hosts. Some protozoa have life stages alternating between proliferative stages (e.g., trophozoites) and dormant cysts. As cysts, protozoa can survive harsh conditions, such as exposure to extreme temperatures or harmful chemicals, or long periods without access to nutrients, water, or oxygen for a period of time. The ability of protozoa to thrive under extreme environments contributes to their ability to evade immune system responses, drug therapies and survive for prolonged periods of time before infection. Being a cyst enables parasitic species to survive outside of a host, and allows their transmission from one host to another. When protozoa are in the form of trophozoites they actively feed. The conversion of a trophozoite to cyst form is known as encystation, while the process of transforming back into a trophozoite is known as excystation.

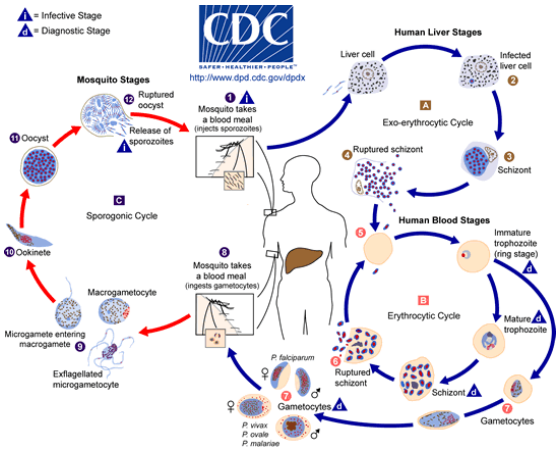

Figure: **Malaria Life Cycle**: Example of a life cycle promoting pathogenicity of a protozoa, specifically the malaria parasite.

Protozoa such as the malaria parasites (Plasmodium spp.), trypanosomes, and leishmania are also important as parasites and symbionts of multicellular animals. Examples of human diseases caused by protozoa are: malaria, amoebiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, Chagas disease, leishmaniasis, and dysentery. The life cycle of protozoan are successful based on successful transmission between hosts and host and environment. Infection and disease by protozoan parasites are often times associated with developing countries with poor hygiene and sanitation conditions that may promote transmission of these protozoa.

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14.6C: Helminths

Parasitic worms, often referred to as helminths, are a division of eukaryotic parasites.

Learning Objectives

- List the four groups of parasitic worms (helminths), routes of transmission and risk factors

Key Points

- Helminths are worm-like organisms that live and feed off of living hosts, receiving nourishment and protection while disrupting the nutrient absorption of their hosts, which causes weakness and disease.
- Helminths that live inside the digestive tract are called intestinal parasites.
- Helminths often find their way into a host through contaminated food or water, soil, mosquito bites, and sexual acts.
- Response to worm infection in humans is a Th2 response in the majority of cases.

Key Terms

- **helminth**: A parasitic roundworm or flatworm.
- **lymphatic system**: In mammals, including humans, a network of lymph vessels and lymph nodes that transport fluid, fats, proteins, and lymphocytes to the bloodstream as lymph, and remove microorganisms and other debris from tissues.

Parasitic worms, often referred to as helminths, are a division of eukaryotic parasites. They are worm-like organisms that live and feed off of living hosts, receiving nourishment and protection while disrupting the nutrient absorption of their hosts, which causes weakness and disease. Those that live inside the digestive tract are called intestinal parasites. They can live inside humans as well as other animals.



Figure: **Hookworms**: The hookworms attached to the intestinal mucosa.

Parasitic worms belong to four groups:

- Monogeneans
- Cestodes (tapeworms)
- Nematodes (roundworms)
- Trematodes (flukes)

Helminths often find their way into a host through contaminated food or water, soil, mosquito bites, and even sexual acts. Poorly washed vegetables eaten raw may contain eggs of nematodes such as Ascaris, Enterobius, Thichuris, and or cestodes such as Taenia, Hymenolepis, and Echinococcus. Plants may also be contaminated with fluke metacercaria, such as Fasciola. Schistosomes and nematodes such as hookworms (Ancylostoma an Necator) and Strongyloides can penetrate the skin. Finally, Wuchereria, Onchocerca, and Dracunculus are transmitted by mosquitoes and flies.

Populations in the developing world are at particular risk for infestation with parasitic worms. Risk factors include the following:

- Inadequate water treatment
- Use of contaminated water for drinking, cooking, washing food, and irrigation
- Undercooked food of animal origin
- Walking barefoot

Simple measures—such as use of shoes, soaking vegetables with 1.5% bleach, adequate cooking of foods (not microwaving), and sleeping under mosquito-proof nets—can have a strong impact on prevention.

Response to worm infection in humans is a Th2 response in the majority of cases. Inflammation of the gut may also occur, resulting in cyst-like structures forming around the egg deposits throughout the body. The host's lymphatic system is also increasingly taxed the longer helminths propagate, as they excrete toxins after feeding. These toxins are released into the intestines and absorbed by the host's bloodstream, making the host susceptible to more common diseases such as seasonal viruses and bacterial infections.

Parasitic worms have been used as a medical treatment for various diseases, particularly those involving an overactive immune response. As humans have evolved with parasitic worms, proponents argue that they are needed for a healthy immune system. Scientists are looking to see if there is a connection between the prevention and control of parasitic worms and the increase in allergies such as hay-fever in developed countries. Parasitic worms may be able to damp down the immune system of their host, making it easier for them to live in the intestine without coming under attack. This may be one mechanism for their proposed medicinal effect.

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14.6D: Algae

Algae can act as pathogens like any other microbe.

Learning Objectives

- Discuss the various types of pathogenic algae

Key Points

- While algal blooms can lead to negative consequences, the effect of an algal bloom are often indirect, the alga is not directly infecting a host.
- Cephaleuros are a genus of parasitic alga which infect plants, causing red rust, which affects many commercial crops that humans consume.
- Prototheca are a type of green alga that lack chlorophyll, that can infect mammals including humans causing the disease protothecosis.
- To some degree the distribution of algae is subject to floristic discontinuities caused by geographical features, such as Antarctica, long distances of ocean, or general land masses.

Key Terms

- **thalloid**: Of a plant, alga, or fungus lacking complex organization, especially lacking distinct stems, roots, or leaves.
- **alga**: any of many aquatic photosynthetic organisms, whose size ranges from a single cell to giant kelps and whose form is very diverse
- **basionym**: An earlier valid scientific name of a species that has since been renamed and from which the new name is partially derived.



Figure: **Cephaleuros virescens**: Infestation of the algal leaf spot (Cephaleuros virescens) on ther southern magnolia (Magnolia grandiflora); Green-orange algal spots or “green scruf” on leaf surface. The grayish-white and darker “crusts” are lichens of the genus Strigula resulting from fungal colonization of the alga.

Algae, are not normally considered common pathogens. Algal blooms are often associated with negative impacts on humans and the surrounding environment in which they occur. A harmful algal bloom (HAB) is an algal bloom that causes negative impacts to other organisms via production of natural toxins, mechanical damage to other organisms, or by other means. HABs are often associated with large-scale marine mortality events and have been associated with various types of shellfish poisonings. However, the damage to other organisms is not due to the algae infecting a host but rather indirectly excreting a toxin, or in some cases blocking out light or competing for resources.

However notable examples of algae acting as pathogens are known. For example Cephaleuros which is a genus of parasitic thalloid alga comprising approximately 14 species. Its common name is red rust. Chrooderma is its basionym. Specimens can reach around 10 mm in size. Dichotomous branches are formed. The alga is parasitic on some important economic plants of the tropics and

subtropics such as tea, coffee, mango and guava causing damage limited to the area of algal growth on leaves (algal leaf spot), or killing new shoots, or disfiguring fruit. Members of the genera may also grow with a fungus to form a lichen that does not damage the plants.

Examples of algae acting as a mammalian pathogen are known as well, notably the disease Protothecosis. Protothecosis is a disease found in dogs, cats, cattle, and humans caused by a type of green alga known as Prototheca that lacks chlorophyll. It and its close relative Helicosporidium are unusual in that they are actually green algae that have become parasites.The two most common species are Prototheca wickerhamii and Prototheca zopfii. Both are known to cause disease in dogs, while most human cases are caused by P. wickerhami. Prototheca is found worldwide in sewage and soil. Infection is rare despite high exposure, and can be related to a defective immune system. In dogs, females and Collies are most commonly affected. The first human case was identified in 1964 in Sierra Leone.

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Thumbnail: Sir Charles Bell’s portrait of a soldier dying of tetanus.

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SECTION OVERVIEW

15.1: Diagnosing Microbial Diseases

Topic hierarchy

15.1A: Diagnosing Microbial Diseases

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15.1A: Diagnosing Microbial Diseases

Learning Objectives

- Compare and contrast the various methods used to diagnose microbial diseases: microbial culture, microscopy, biochemical tests and molecular diagnostics

The process of identifying infectious diseases is complex and requires identification of the agent through direct or indirect means. In regards to many microbial diseases, it is often difficult to diagnose an individual based on clinical presentation. As such, further testing is required. The methods used to diagnose microbial disease include microbial culture, microscopy, biochemical tests, and molecular diagnostics.

Microbial Culture

The first tool in diagnosing microbial disease is microbial cultures. The sample is obtained from the infected individual and tested for the presence of an infectious agent or microbe that is capable of growing in specific media. It is critical to isolate the infectious agent in a pure culture containing *only* the infectious bacteria. The most common method to isolate individual cells and produce a pure culture is to prepare a streak plate. The streak plate method is a way to physically separate the microbial population, and is done by spreading the inoculate back and forth with an inoculating loop over the solid agar plate. Upon incubation, colonies will arise and single cells will have been isolated from the biomass.

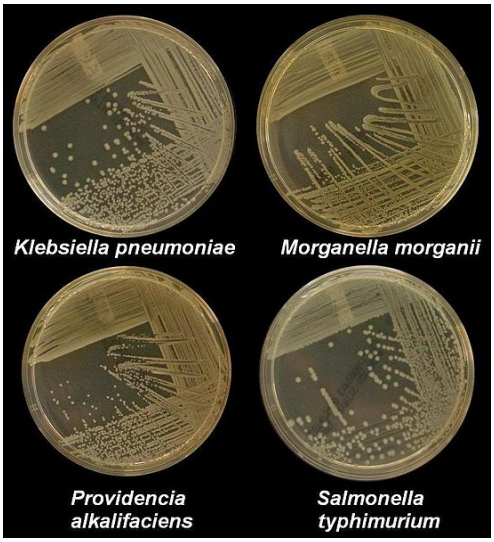

Figure: **Common bacteria that cause disease in humans**: This represents four nutrient agar plates with various bacterial species represented. The use of plates for microbial culture aid in identification of microbes based on size, shape, colony formation and nutrient requirement.

It is established that most pathogenic bacteria can be grown on nutrient agar, and the addition or subtraction of specific nutrients can aid in further identification. The use of microbial cultures is common to help in the clinical identification of pathogenic microbes. However, there are specific classes of microbe that require culture within live animals. The bacteria *Mycobacterium leprae* is such a microbe, as it can only be cultured in animals.

There are also specific types of infectious agents that require the use of xenodiagnosis to promote growth. The parasite responsible for Chagas disease, *Trypanosoma cruzi*, requires a vector for diagnosis. For example, an uninfected reduviid bug is used to feed from an individual suspected of having Chagas. Once the blood is taken, the bug will be analyzed for *Trypanosoma cruzi* growth.

Microscopy

An additional tool utilized for microbial disease diagnosis is microscopy. To ensure proper identification of a pathogen, microscopy, in combination with biochemical staining techniques, is often used to ensure definitive identification. Biochemical staining techniques that are used to aid in identification include stains such as Giemsa, crystal violet, and other stains that help distinguish between gram positive and gram negative.

Biochemical Tests

Biochemical tests are also used to help in microbial disease diagnosis. They will specifically test for metabolic and enzymatic products that an infectious agent may use. Biochemical tests will also test for fermentation products, acids, alcohol or gases that may be products of metabolic pathways.

Molecular Diagnostics

The identification of infectious agents is now often done by using molecular based techniques such as polymerase chase reactions (PCR). PCR allows for the identification and testing for nucleic acids which are specific to the infectious agent. The need of an infectious agent to amplify its own nucleic acids to ensure successful infection has allowed us to use PCR to detect the presence of these nucleic acids. In combination with the advances made in genome sequencing, the tools and information needed to establish PCR as the gold-standard for diagnosing microbial disease is present.

Key Points

- Microbial culture is a technique utilized to help in microbial disease diagnosis and can include nutrient plates, liquid cultures, culture within live animals, and use of a vector as well.
- Microscopy is an additional technique used to identify pathogenic microbes by utilizing specialized stains to help identification and characterization based on specific principes.
- Biochemical tests are used to help identify pathogenic microbes and focus on metabolic or enzymatic products that are specific to microbes based on their metabolic pathways.

Key Terms

- **xenodiagnosis**: The diagnosis of an infectious disease by exposure to a vector of that disease and performing analysis on the vector for the disease.

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SECTION OVERVIEW

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15.10A: Chagas Disease (American Trypanosomiasis)

Learning Objectives

- Describe the life cycle of Trypanosoma cruzi

Chagas disease, also known as American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*. It is transmitted to humans via the reduviid bug (the “kissing bugs”), and is therefore characterized as a zoonotic disease.

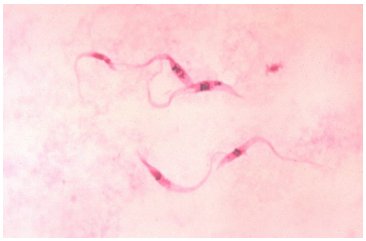

Figure: **Trypanasoma cruzi**

Chagas disease is similar to African sleeping sickness which is caused by the African trypanosome. The risk factors for Chagas disease include living where reduviid bugs live, including areas of Central and South America. In addition, it is possible to obtain Chagas via blood transfusion from an individual with the active disease.



Figure: **Reduviid bug**: In Chagas-endemic areas, the main mode of transmission is through an insect vector called a triatomine or reduviid bug.The bugs emerge at night, when the inhabitants are sleeping. Because they tend to feed on people’s faces, triatomine bugs are also known as “kissing bugs.” After they bite and ingest blood, they defecate on the person. Triatomines pass T. cruzi parasites (called trypomastigotes) in feces left near the site of the bite wound.

The reduviid bug itself becomes infected by feeding on the blood of an already-infected person or animal. The bugs are nocturnal, emerge at night and typically feed on an individual’s face. The bug then proceeds to defecate on the person, passing *Trypanosoma cruzi* parasites in its feces in posterior station infection. These parasites surround the bite wound and, when the bite is scratched, the parasites are able to pass into the host. The reduviid bud often bites the tender skin around the eyes, leaving a swollen bump called a chagoma or Ramona’s sign.



Figure: **Romaña's sign**: The most recognized marker of acute Chagas disease is called Romaña's sign, which includes swelling of the eyelids on the side of the face near the bite wound or where the bug feces were deposited or accidentally rubbed into the eye.

At this specific stage, the parasites are referred to as trypomastigotes, and these invade the host cells and differentiate into intracellular amastigotes where they continue to multiply by binary fission. These amastigotes then differentiate into trypomastigotes which circulate into the bloodstream. At this time, if the infected individual is re-bitten by a reduviid bug, the cycle will start again.

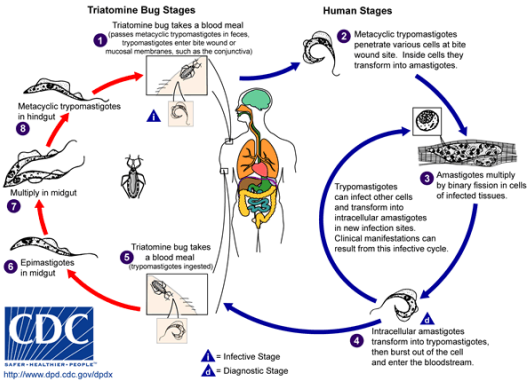

Figure: **Lifecycle of Trypanasoma cruzi**: Chagas disease can be characterized by two phases: acute and chronic. The acute phase is characterized by mild symptoms which include fever, swelling of an eye or area surrounding the insect bite. However, the acute phase will enter remission and then, over time, additional symptoms will develop that include: constipation, gastrointestinal issues, heart failure, abdominal pain and difficulties swallowing.

Chagas disease can be characterized by two phases: acute and chronic. The acute phase is presents with mild symptoms which include: fever, swelling of an eye and/or the area surrounding the insect bite.

The acute phase will then enter remission and, over time, additional symptoms will develop that include: constipation, gastrointestinal issues, heart failure, abdominal pain and difficulties swallowing. It can sometime take upwards of 20 years from the time of infection for these later heart and digestive issues to present. American trypanosomiasis causes megacolon and megaesophagus and an enlarged heart in pediatric patients and is very serious.

Key Points

- Chagas disease is prevalent in areas with reduviid bugs such as Central and South America.
- Chagas disease is transmitted via a vector, the reduviid bug, which becomes infected when it bites an already-infected individual.
- The life cycle of Trypanosoma cruzi requires two hosts, the reduviid bug and the human or animal host.

Key Terms

- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.

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15.10B: Toxoplasmosis

Learning Objectives

- Compare and contrast: acute and latent toxoplasmosis and outline the life cycle of the protazoan that causes it

Toxoplasmosis is an infection caused by the parasite *Toxoplasma gondii.* Toxoplasmosis is found in humans worldwide, but the definitive hosts are cats. Humans may become infected as a result of infected blood transfusions, organ transplants, ingesting contaminated soil, raw or undercooked meat, and most commonly from the careless handling of cat litter, which can lead to accidental ingestion of the parasite. Toxoplasmosis can also be passed from an infected mother to her baby via the placenta (transplacentally). Symptoms that may occur from toxplasmosis include: enlarged lymph nodes, headache, fever, muscle pain, and sore throat. Individuals with immunocompromised or weakened systems display more severe symptoms, such as: confusion, fever, headache, blurred vision and seizures. The three categories of toxoplasmosis include acute, latent, and cutaneous toxoplasmosis.

Symptoms

Acute toxoplasmosis is characterized by swollen lymph nodes found in the neck or under the chin, followed by the axillae, and the groin area. Enlarged lymph nodes will occur at different times after the initial infection. Latent toxoplasmosis is characterized by the formation of cysts in both the nervous and muscle tissue due to the bradyzoite form of the parasite. Often times, individuals infected with latent toxoplasmosis do not present with symptoms, as the infection enters a latent phase. In individuals with cutaneous toxoplasmosis, skin lesions will occur due to the tachyzoite form of the parasite and its presence in the epidermis.

Hosts, Life Cycle

The known definitive hosts for *Toxoplasma gondii* are members of family Felidae (domestic cats and their relatives). In the life cycle of this parasite, unsporulated oocysts are shed in the cat's feces. The cat will shed large numbers of these cysts over a short period of time. The oocysts will then take 1-5 days to sporulate in the environment and become infective. The intermediate hosts in nature (including birds and rodents) become infected after ingesting contaminated soil, water, or plant material. The oocysts, upon ingestion, will transform into tachyzoites, which will localize in the neural and muscle tissue. After localizing to these sites, they will develop into tissue cyst bradyzoites. Cats, can become infected after consuming intermediate hosts that are infected with tissue cysts or by ingesting sporulated oocysts.

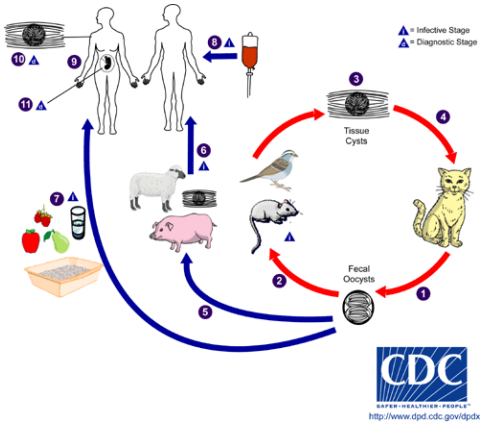

Figure: **Toxoplasmosis Life Cycle**: Overview of the life cycle of Toxoplasmosis godii.

Key Points

- Cats are the definitive hosts for Toxoplasma gondii and are the primary source of infection to humans.
- Toxoplasmosis can occur in either acute, latent or cutaneous forms.
- Toxoplasmosis is found worldwide and can be transmitted by eating undercooked meat of animals which may contain cysts, ingesting contaminated food or water, transplacentally or from coming in contact with infected cat feces.

Key Terms

- **definitive host**: a host in which the parasite reaches maturity and, if possible, reproduces sexually
- **axillae**: The armpit
- **transplacental**: Through or across the placenta

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15.10C: Malaria

Learning Objectives

- Reconstruct the route of transmission and life cycle for Plasmodium species that cause malaria and describe its symptoms

Malaria is a parasitic disease that is caused by the bite of an infected Anopheles mosquito. Malaria can be transmitted from mother to baby and by blood transfusions. The Anopheles mosquito transmits the parasites, called sporozoites, upon biting the hosts, into the bloodstream to the liver, where the parasites continue their life cycle. In the liver, the parasites mature and release another form called merozoites, which enter the bloodstream and infect the red blood cells. In the red blood cells, they develop into ring forms called trophozoites and schizonts that in turn, produce further merozoites. Upon infection of the red blood cells, the parasite is able to multiply within the cell, break open and continue infecting additional red blood cells. The symptoms occur in a cyclical manner every 48-72 hours. Malaria is characterized by the development of symptoms that include high fevers, shaking chills, flu-like symptoms, and anemia. The symptoms that persist due to parasitic infection are a result of the release of merozoites into the bloodstream, destruction of the red blood cells and the free circulation of large amounts of hemoglobin in the red blood cells due to disruption.

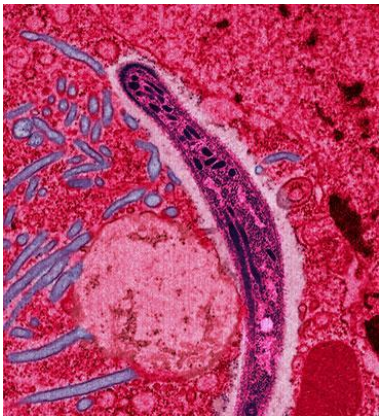

Figure: **The malaria plasmodium**: Malaria is transmitted to people and animals by mosquitoes. Malarial sporozoites develop inside oocysts and are released in large numbers into the hemocoel of Anopheles stephensi mosquitoes. This false-colored electron micrograph shows a sporozoite migrating through the cytoplasm of midgut epithelia.

The five types of malaria parasites include species of Plasmodium. The fives species include: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and *Plasmodium knowlesi*. *Plasmodium falciparum* is responsible for the majority of deaths caused by infection and *Plasmodium vivax, ovale and malariae*cause a milder form of malaria. The species, *Plasmodium knowlesi*, commonly causes malaria in macaques but can also cause severe infections in humans.

Malaria is common in temperate climates and the Centers for Disease Control and Prevention (CDC) estimates 300-500 million cases each year. In addition, it is estimated that 1 million people die from it each year as well. Malaria is typically diagnosed by microscopic examination of blood or with antigen-based rapid diagnostic tests. Disease transmission can be reduced by preventing mosquito bites through the use of mosquito nets and insect repellents. However, the mosquitoes which transmit malaria have begun to develop resistance to insecticides and the parasite itself has developed resistance to commonly used antibiotics. As a result of increased resistance, it is extremely difficult to contain the spread of this disease.

Key Points

- The five common species of Plasmodium that cause malaria include: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi.
- Mosquitoes transmit the protists by injecting sporozoites into the bloodstream of humans.
- The sporozoites injected into the bloodstream, travel to the liver where they multiply into merozoites, rupture the liver cells, and then return to the bloodstream.
- A mosquito, upon feeding off an already infected individual, will carry the protists and become infectious.
- The symptoms of malaria can present in a cyclic manner.

Key Terms

- **merozoites**: the organisms formed by multiple fission of a sporozoite within the body of the host.
- **antigen**: A substance that induces an immune response, usually foreign.
- **sporozoites**: Any of the minute active bodies into which a sporozoan divides just before it infects a new host cell.

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15.10D: Leishmaniasis

Learning Objectives

- Outline the life cycle of Leishmania and distinguish between cutaneous or viseral leishmaniasiss within the Ideal Gas Law

Leishmaniasis is a disease transmitted by the bite of a female sandfly. There various types of leishmaniasis that exist including cutaneous leishmaniasis, systemic, or visceral leishmaniasis. Cutaneous leishmaniasis is characterized by infection of the skin and mucous membranes. The symptoms include skin sores which present at the site of the sandfly bite. In addition, cutaneous leishmaniasis includes breathing difficulty, stuffy nose, runny nose, nose bleeds, swallowing difficulty and ulcers in the mouth, tongue, gums, lips, nose, and inner nose. Systemic or visceral leishmaniasis present as an infection of the entire body. There is a delay of symptoms, ranging from 2-8 months post bite, and the effects on the immune system can result in deadly complications. The parasites damage the immune system by targeting the disease-fighting cells. Symptoms present much more quickly in children and include a cough, diarrhea, fever, and vomiting. In adults, there is fatigue, weakness, loss of appetite, abdominal pain, night sweats, fever, weight loss, and changes in the color and texture of the skin. In combination, cutaneous and visceral leishmaniasis are caused by more than 20 different leishmanial species.

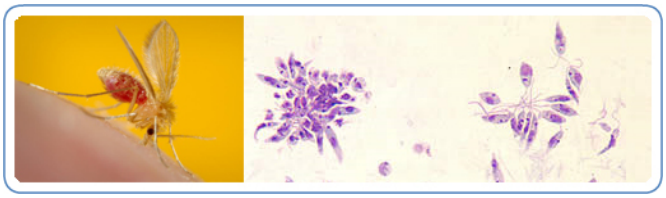

Figure: **Leishmaniasis**: A Phlebotomus papatasi sand fly that transmits one type of leishmaniasis, next to an image of Leishmania sp. promastigotes from culture. This is the stage of the parasite that occurs inside the mid-gut of the sand fly.

Leishmaniasis is vector-borne because it is transmitted via a bite from a sandfly. The sandflies that cause leishmaniasis are infected by an obligate intracellular protozoa of the genus Leishmania. The species of Leishmania that can cause leishmaniasis include: L. donovani complex with 2 species (L. donovani, L. infantum, also known as L. chagasi); the L. mexicana complex with 3 main species (L. mexicana, L. amazonensis, and L. venezuelensis); L. tropica; L. major; L. aethiopica; and the subgenus Viannia with 4 main species (L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis, and L. (V.) peruviana). These various species are indistinguishable via morphology but can be identified using advanced techniques such as isoenzyme analysis.

Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies which can transmit the infection Leishmania. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals. Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages and transform into amastigotes. Amastigotes multiply in infected cells and affect different tissues, depending in part on which Leishmania species is involved. These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on infected hosts when they ingest macrophages infected with amastigotes. In the sandfly's midgut, the parasites differentiate into promastigotes, which multiply, differentiate into metacyclic promastigotes, and migrate to the proboscis.

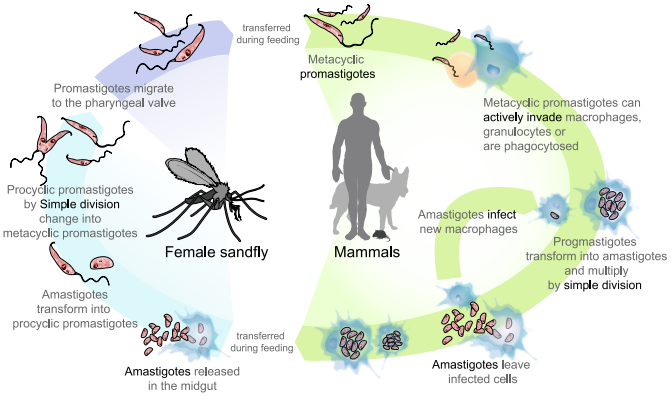

Figure: **Leishmaniasis life cycle**: Leishmaniasis is a vector-borne disease and is transmitted by the sand fly.

Key Points

- Leishmaniasis is a vector-borne disease and is transmitted by the sand fly.
- Cutaneous leishmaniasis is the most common form of leishmaniasis and symptoms include skin sores.
- Visceral leishmaniasis is more severe and is characterized by the migration of parasites to the vital organs and tissues.

Key Terms

- **visceral**: of or relating to the viscera – the internal organs of the body
- **cutaneous**: of, relating to, existing on, or affecting the exterior skin; especially the cutis
- **phagocytosis**: the process by which a cell incorporates foreign particles intracellularly.

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15.10E: Babesiosis

Learning Objectives

- Outline the life cycle of the Babesia microti parasite that causes babesiosis

Babesiosis is a malaria-like parasitic disease caused by Babesia. Babesia is a genus of protozoal piroplasms which are characterized by their ability to divide by binary fission. Also, protozoal piroplasms are sporozoan parasites, and so they possess both sexual and asexual phases. The piroplasm is categorized under Phylum Apicomplexa and specifically, Babesia, is a parasite transmitted via a tick vector. Many of the cases of Babesia infection are asymptomatic but can include mild fevers and diarrhea. The more severe cases are plagued with high fevers, shaking chills, and severe anemia, similar to symptoms seen in individuals infected with malaria. If the disease progresses without treatment and it is severe, the infected individual can suffer from organ failure and adult respiratory distress syndrome. Recently, there has been an increase in babesiosis diagnosis due to an increase in the number of individuals with immunodeficiencies coming into contact with ticks.

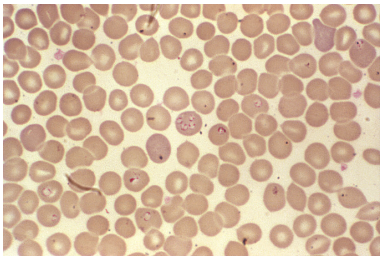

Figure: **Babesia parasites**: Other hemoprotozoan parasites such as these Babesia sp. resemble Plasmodium falciparum organisms. Though developmentally the Babesia spp. organisms resemble Plasmodium falciparum, these parasites present several distinguishing features: they vary more in shape and in size; and they do not produce pigment.

The life cycle of Babesia parasites is characterized by their ability to undergo reproduction in the erythrocytes. These parasites, within the red blood cells, form a distinctive structure called a “Maltese Cross” that is composed of four attached merozoites undergoing asexual budding. This asexual process results in hemolytic anemia. The Babesia microti life cycle includes two hosts, a rodent, primarily the white-footed mouse, and a tick.

During a blood meal, the tick introduces sporozoites into the mouse host. The sporozoites enter the erythrocytes and undergo asexual reproduction as previously mentioned. In the blood, the parasites will then differentiate into male and female gametes. The definitive host, the tick, will then ingest both types of gametes (upon another blood meal). The gametes will unite and undergo a sporogonic cycle resulting in sporozoite. The humans play a role in this cycle if they are bitten by an infected tick. The tick will introduce the sporozoites and the cycle will proceed. Diagnosis of babesiosis is performed using a Giemsa-test for parasitic identification. The “Maltese Cross” is observed on blood films and both serological testing for antibodies and PCR testing for Babesia from the peripheral blood is performed.

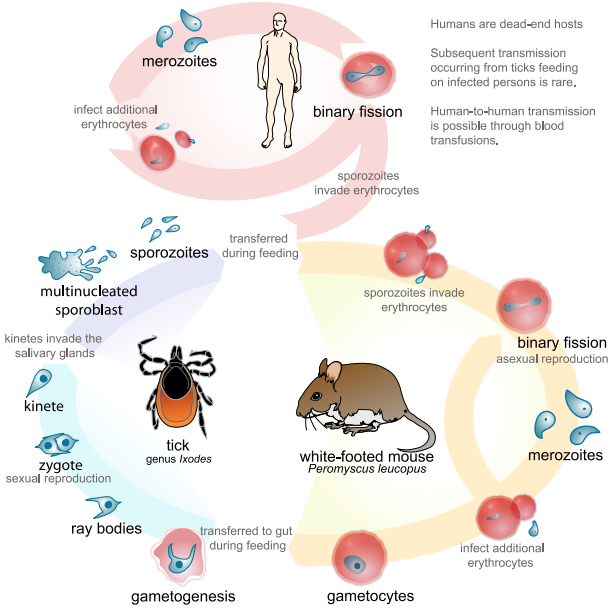

Figure: **The life cycle of Babesia parasites**: Babesia is capable of undergoing both sexual and asexual reproduction in its life cycle. Ticks transmit the human form of Babesiosis, so it often presents with other tick-borne illnesses such as Lyme disease.

Key Points

- Babesia, the parasite, is capable of undergoing both sexual and asexual reproduction in its life cycle.
- A majority of individuals infected with babesiosis are asymptomatic but severe cases display malaria-like symptoms which include high fevers, chills, shakes, and hemolytic anemia.
- A definitive characteristic of Babesia infection is the formation of a “Maltese Cross” structure within the erythrocytes that represents the asexual budding of four attached merozoites.

Key Terms

- **piroplasms**: a protozoan parasite of the phylum Apicomplexa.
- **sporozoite**: any of the minute active bodies into which a sporozoan divides just before it infects a new host cell
- **hemolytic**: producing hemolysis; destroying red blood cells

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15.10F: Schistosomiasis

Learning Objectives

- Outline the life cycle of the trematodes of the genus Schistosoma that cause schistosoomiasis

Schistosomiasis is a parasitic disease caused by various species of trematodes or "flukes," which are of the genus *Schistosoma*. For parasites categorized as schistosomes, the snail is the intermediary agent between the mammalian hosts. Schistosomiasis is common in countries that lack the facilities to maintain proper water supplies and sanitation facilities. These supplies and facilities are often exposed to contaminated water that contains infected snails. Individuals infected with schistosomiasis display chronic illness that can result in the damage of internal organs and in children, targets growth and cognitive development. Children will often acquire the disease by swimming or playing in contaminated water. Upon contact with contaminated water, the parasitic larvae can penetrate the skin and mature within the organ tissues.

The life cycle of the various human schistosomes is similar. The parasitic eggs are released into the environment from already-infected individuals and hatch on contact with water, releasing free-swimming miracidia. These infect freshwater snails by penetrating their skin. The site of penetration will promote the transformation of the miracidium into a primary sporocyst. This contains germ cells which will divide to produce secondary sporocysts. In turn, these migrate to the snails' hepatopancreas and the germ cells, now present within the secondary sporocysts, will divide to form thousands of new parasites called *cercariae*. These are the larvae capable of infecting mammals.

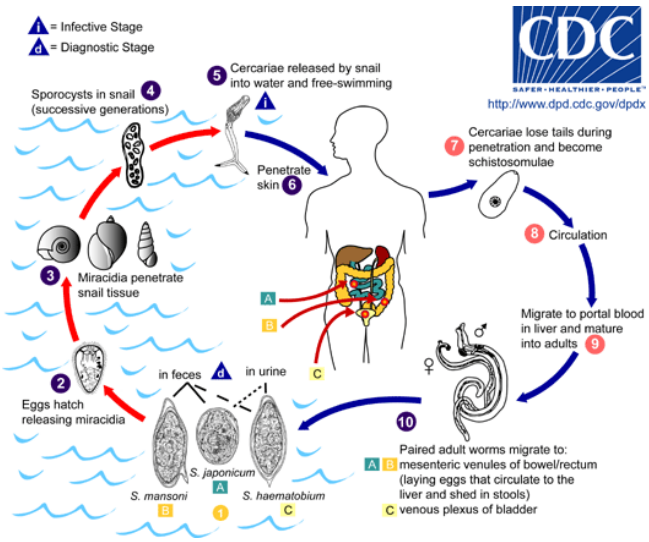

Figure: **Schistosome Life Cycle**: Overview of Schistosome generalized life cycle.

Interestingly, the cercariae are released from the snail host in a circadian rhythm and depend on ambient temperature and light. Penetration of the human skin occurs after the cercariae have attached to and explored the skin. The parasite secretes enzymes that break down the skin's protein to enable penetration of the cercarial head through the skin. As the cercaria penetrates the skin, it transforms into a migrating schistosomulum stage.

The various species which can infect humans include:

- *Schistosoma mansoni*, *Schistosoma intercalatum*: cause intestinal schistosomiasis
- *Schistosoma haematobium*: causes urinary schistosomiasis
- *Schistosoma japonicum*, *Schistosoma mekongi:* cause Asian intestinal schistosomiasis
- *Avian schistosomiasis* species: cause swimmer's itch and clam digger itch

Key Points

- For parasites categorized as schistosomes, the snail is the intermediary agent between the mammalian hosts.
- Schistosomiasis is common in countries that lack the facilities to maintain proper water supplies and sanitation facilities. These supplies and facilities are often exposed to contaminated water that contains infected snails.

- Individuals infected with schistosomiasis display chronic illness that can result in the damage of internal organs and in children, affects target growth and cognitive development.

Key Terms

- **hepatopancreas**: An organ of the digestive tract of arthropods and fish which provides the function which in mammals is provided separately by the liver and pancreas.

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15.10G: Swimmer's Itch

Swimmer's itch is a result of an immune reaction in response to the penetration of the skin by a schistosome.

Learning Objectives

- Outline the general life cycle of the Schistosomatidae parasite that causes schistosome cercarial dermatitis

Key Points

- Swimmer's itch is commonly referred to as lake itch, duck itch, cercarial dermatitis and Schistosome cercarial dermatitis.
- The cercaria, the larvae stage of the parasite, will accidentally penetrate the skin of a human host and die within the skin. The cercaria cannot continue the life cycle in a human and requires its normal host, a waterfowl.
- The penetration of the skin by the cercaria result in an inflammatory immune reaction that causes itchy spots and raised papules in humans.

Key Terms

- **swimmer's itch**: Swimmer's itch, also known as lake itch, duck itch, cercarial dermatitis, and Schistosome cercarial dermatitis, is a short-term, immune reaction occurring in the skin of humans that have been infected by water-borne schistosomatidae.
- **papules**: A small, inflammatory, irritated spot on skin; similar in appearance to a pimple, without containing pus.
- **cercaria**: The parasitic larva of trematodes; its tail disappears when adult.

Swimmer's itch is a condition often referred to as lake itch, duck itch, cercarial dermatitis and Schistosome cercarial dermatitis. It is caused by an immune response that is activated upon the entry of a water-borne flatworm parasite named schistosomatidae into the skin. The schistosomatidae results in an immune reaction in the skin that results in itchy, raised papules that occur within hours of infection.

There are numerous types of flatworm parasites within the family Schistosomatidae that can cause swimmer's itch. The schistosomatidae which are responsible for swimmer's itch include the genera Trichobilharzia and Gigantobilharzia. A species that is often implicated in cases of cercarial dermatitis is Austrobilharzia variglandis. The hosts of this species are ducks and the snail is the intermediate host for this species.

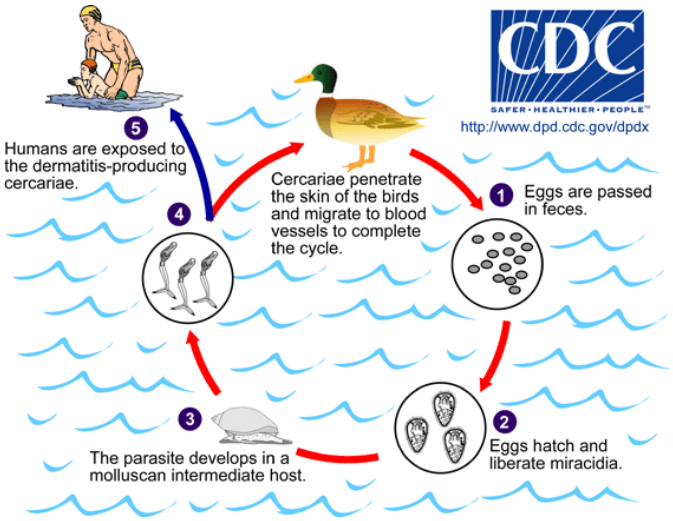

Figure: **Life cycle of schistosomes**: An overview of the life cycle of a schistosome and how they can cause swimmer's itch in humans.

The life cycle of these parasites is characterized by their use of both freshwater snails and vertebrates as hosts. More specifically, waterfowl are used as the vertebrate host. During the life stage of these parasites, the larvae of the parasite, cercaria, exit the water snails and can accidentally come into contact with the skin of a swimmer. Upon contact with the skin of the swimmer, the cercaria will penetrate the skin and immediately die in the skin. Interestingly, the cercaria are unable to survive within a human host and cause infection. The symptoms and reactions exhibited in individuals diagnosed with swimmer's itch are a result of the dead cercaria larvae.

If indeed the cercaria encounter a water bird, their normal host, the cercaria will penetrate the skin of the birds and migrate to the blood vessels to complete the cycle. For completion of the cycle, adult worms will form in the blood vessels and produce eggs which are passed in the feces. The eggs, upon exposure to water, will hatch into a miracidium that is ciliated. This form in the life cycle infects the snail intermediate host. In turn, the cercaria which are responsible for swimmer's itch are produced.

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SECTION OVERVIEW

15.11: Microbial Diseases of the Respiratory System

Topic hierarchy

15.11A: Functional Anatomy of the Respiratory System

5.11B: Airborne Transmission of Disease

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15.11A: Functional Anatomy of the Respiratory System

The respiratory system include lungs, airways and respiratory muscles. Ventilation is the rate at which gas enters or leaves the lung.

Learning Objectives

- Summarize the the functional anatomy of the respiratory system

Key Points

- Ventilation occurs under the control of the autonomic nervous system from parts of the brain stem—the medulla oblongata and the pons —that together form the respiration regulatory center.
- The three types of ventilation are minute ventilation, alevolar ventilation, and dead space ventilation.
- Inhalation is initiated by the diaphragm and supported by the external intercostal muscles. Additional accessory muscles include sternocleidomastoid, platysma, the scalene muscles of the neck, pectoral muscles, and the latissimus dorsi.
- When the diaphragm contracts, the ribcage expands and the contents of the abdomen are moved downward, resulting in a larger thoracic volume and negative pressure (with respect to atmospheric pressure) inside the chest.
- Exhalation is generally a passive process since the lungs have a natural elasticity; they recoil from the stretch of inhalation and air flows back out until the pressures in the chest and the atmosphere reach equilibrium.
- Gas exchange occurs at the alveoli, the tiny sacs that are the basic functional component of the lungs. The alveoli are interwoven with capillaries that connect to the larger bloodstream.

Key Terms

- **elastic recoil**: The lungs' rebound from the stretch of inhalation that passively removes air from the lungs during exhalation.
- **Dead space**: Any space in the airways that is not involved in alveolar gas exhange, such as the conducting zones.
- **ventilation**: The bodily process of breathing, the inhalation of air to provide oxygen, and the exhalation of spent air to remove carbon dioxide.

The Respiratory System

The primary function of the respiratory system is gas exchange between the external environment and an organism 's circulatory system. In humans and other mammals, this exchange balances oxygenation of the blood with the removal of carbon dioxide and other metabolic wastes from the circulation.

As gas exchange occurs, the acid-base balance of the body is maintained as part of homeostasis. If proper ventilation is not maintained, two opposing conditions could occur: respiratory acidosis (a life threatening condition) and respiratory alkalosis.

At the molecular level, gas exchange occurs in the alveoli—tiny sacs which are the basic functional component of the lungs. The alveolar epithelial tissue is extremely thin and permeable, allowing for gas exchange between the air inside the lungs and the capillaries of the blood stream. Air moves according to pressure differences, in which air flows from areas of high pressure to areas of low pressure.

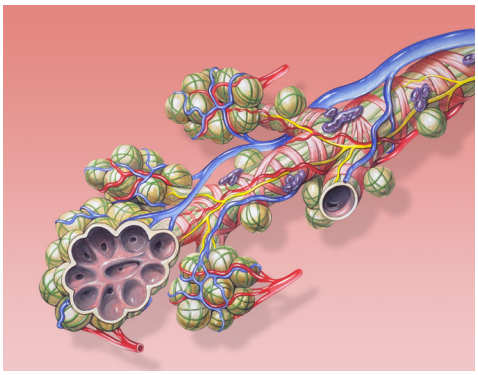

Figure: **Bronchial anatomy**: The pulmonary alveoli are the terminal ends of the respiratory tree, outcropping from either alveolar sacs or alveolar ducts, which are both sites of gas exchange with the blood.

The Ventilation Rate

In respiratory physiology, ventilation rate is the rate at which gas enters or leaves the lung. There are several different terms used to describe the nuances of the ventilation rate.

- Minute Ventilation (V_E): The amount of air entering the lungs per minute. It can be defined as tidal volume (the volume of air inhaled in a single breath) times the amount of breaths in a minute.
- Alveolar Ventilation (V_A): The amount of gas per unit of time that reaches the alveoli (the functional part of the lungs where gas exchange occurs). It is defined as tidal volume minus dead space (the space in the lungs where gas exchange does not occur) times the respiratory rate.
- Dead Space Ventilation (V_D): The amount of air per unit of time that doesn't reach the alveoli. It is defined as volume of dead space times the respiratory rate.

Dead space is any space that isn't involved in alveolar gas exchange itself, and it typically refers to parts of the lungs that are conducting zones for air, such as the trachea and bronchioles.

If someone breathes through a snorkeling mask, the length of their conducting zones increases, which increases dead space and reduces on alveolar ventilation. Feedback mechanisms increase the ventilation rate in such a case, but if dead space becomes too great, they won't be able to counteract the effect.

The ventilation rate is controlled by several centers of the autonomic nervous system in the brain, primarily the medulla and the pons.

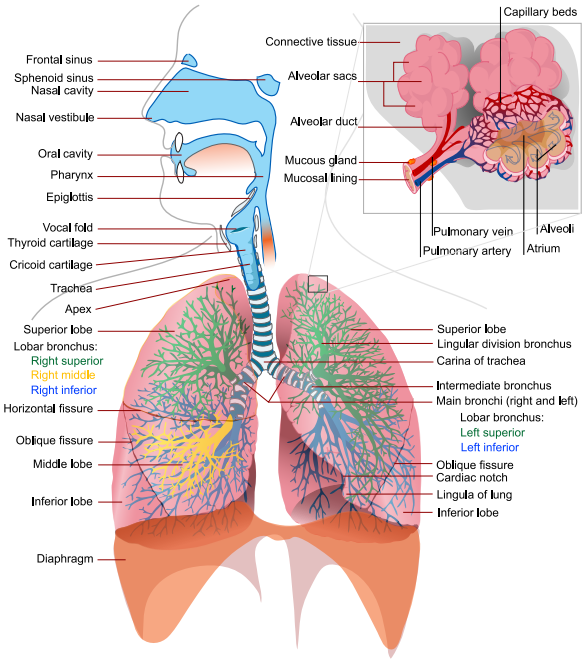

Figure: **The human respiratory system**: A complete, schematic view of the human respiratory system with its parts and functions.

Mechanisms of Inhalation

Inhalation is initiated by the activity of the diaphragm and supported by the external intercostal muscles. A normal human respiratory rate is 10 to 18 breaths per minute.

During vigorous inhalation (at rates exceeding 35 breaths per minute), or in approaching respiratory failure, accessory muscles—such as the sternocleidomastoid, platysma, and the scalene muscles of the neck—are recruited to help sustain the increased respiratory rate. Pectoral muscles and latissimus dorsi are also accessory muscles for the activity of the lungs.

Under normal conditions, the diaphragm is the primary driver of inhalation. When the diaphragm contracts, the rib cage expands and the contents of the abdomen are moved downward, resulting in a larger thoracic volume and negative pressure (with respect to atmospheric pressure) inside the thorax.

As air moves from zones of high pressure to zones of low pressure, the contraction of the diaphragm allows the air to enter the conducting zone (such as the trachea, bronchioles, etc.), where it is filtered, warmed, and humidified as it flows to the lungs.

Mechanisms of Exhalation

Exhalation is generally a passive process. The lungs have high degree of elastic recoil, so they rebound from the stretch of inhalation and air flows out until the pressures in the lungs and the atmosphere reach equilibrium.

The reason for the elastic recoil of the lung is the surface tension from water molecules on the epithelium of the lungs. A molecule called surfactant (secreted by the alveoli) prevents the surface tension from becoming too great and collapsing the lungs.

Active or forced exhalation is achieved by the abdominal and the internal intercostal muscles. During this process, air is forced or exhaled out. During forced exhalation, as when blowing out a candle, the expiratory muscles, including the abdominal muscles and internal intercostal muscles, generate abdominal and thoracic pressure that force air out of the lungs.

Forced exhalation is often used as an indicator to measure airway health, as people with obstructive lung diseases (such as emphysema, asthma, and bronchitis) will not be able to actively exhale as much as a healthy person because of obstruction in the conducting zones from inhlation, or from a loss of elastic recoil of the lungs.

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5.11B: Airborne Transmission of Disease

Airborne diseases are characterized by diseases that are transmitted through the air via the presence of a pathogen.

Learning Objectives

- Give examples of airborne pathogens and various routes of transmission

Key Points

- Airborne transmission results in the inhalation of pathogens that can affect an individual's respiratory system or the rest of the body.
- Airborne diseases are caused by pathogens which can ride on either dust particles or small respiratory droplets that can stay suspended in the air and travel distances on air currents.
- Airborne diseases are commonly seen in unsanitary household conditions and overcrowded areas, and thrive in areas of poverty and poor hygienic conditions.

Key Terms

- **droplet nuclei**: Droplet nuclei are an important mode of transmission among many infectious viruses such as Influenza A. When viruses are shed by an infected person through coughing or sneezing into the air, the mucus coating on the virus starts to evaporate. Once this mucus shell evaporates the remaining viron is called a droplet nucleus or quanta.

Airborne Transmission of Disease



Figure: **Airborne transmission**: Infection of the respiratory system via airborne transmission.

Airborne diseases are characterized by diseases that are transmitted through the air via the presence of a pathogen. These pathogens can include both viruses and bacteria that are spread by coughing, sneezing, laughing, or through personal contact. The pathogens are capable of traveling distances on air currents when they are present on either dust particles or small respiratory droplets. The airborne transmission that occurs utilizes small particles or droplet nucleithat contains these infectious agents or pathogens. These particles and droplets are capable of remaining suspended in air for extended periods of time. Inhalation of these particles results in respiratory tract infection. The ability of these droplets to remain suspended for long periods of time result in the lack of face-to-face contact for infection. The ability of these pathogens to survive and retain their ability to infect for relatively long periods of time add to the difficulty encountered in their prevention and targeting.

Often times, these airborne pathogens can result in inflammation in the nose, throat, sinuses, and the lungs. The symptoms such as sinus congestion, coughing, and sore throats are examples of inflammation of the upper respiratory airway. Many types of infections that can be a result of airborne transmission include: Anthrax, Chickenpox, Influenza, Measles, Smallpox, and Tuberculosis. Airborne diseases are caused by exposure to a source such as an infected individual or animal.

Airborne transmission of disease is common in unsanitary household conditions and overcrowded areas, and pathogens that are transmitted in this manner thrive in areas of poverty and poor hygienic conditions. For example, tuberculosis is common in individuals from developing areas in the world, adding to 95% of cases worldwide.

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SECTION OVERVIEW

15.12: Bacterial Diseases of the Respiratory System

Topic hierarchy

15.12A: Pharyngitis

15.12B: Scarlet Fever

15.12C: Diphtheria

15.12D: Otitis Media

15.12E: Whooping Cough

15.12F: Tuberculosis

15.12G: Bacterial Pneumonias

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15.12A: Pharyngitis

Pharyngitis is an inflammation of the throat that has many causes, some of which are bacterial infections.

Learning Objectives

- List the symptoms and bacterial causes associated with pharyngitis

Key Points

- In most cases, pharyngitis is caused by a systemic viral infection and is typified by a painful swelling inflammation of the throat. This can cause difficulty swallowing or breathing.
- The most common bacterial cause of pharyngitis is streptococcus.
- Several types of bacteria can cause pharyngitis. The most common and effective treatment for these infections are antibiotics.

Key Terms

- **hemolytic**: producing hemolysis; destroying red blood cells
- **peritonsillar abscess**: Peritonsillar abscess (PTA), also called a quinsy, or abbreviated as a PTA, is a recognized complication of tonsillitis. It consists of a collection of pus beside the tonsil in what is referred to as Peritonsilar space (Peri – meaning surrounding).

Pharyngitis

Pharyngitis is an inflammation of the throat. In most cases, it is quite painful and is the most common cause of a sore throat. Like many types of inflammation, pharyngitis can be acute or chronic. Acute cases are characterized by a rapid onset and, typically, a relatively short course of inflammation. Pharyngitis can result in very large tonsils. This can make swallowing and breathing difficult. It can be accompanied by a cough or fever, for example, if it is caused by a systemic infection. Most acute cases are caused by viral infections (40–80%). The remainder are caused by bacterial infections, fungal infections, or irritants such as pollutants or chemical substances. The treatment of viral causes is mainly symptomatic. Bacterial or fungal causes are often amenable to antibiotics and anti-fungal treatments, respectively.

Bacterial Causes of Pharyngitis

A number of different bacteria can infect the human throat. The most common is Group A streptococcus, but others include Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydophila pneumoniae, and Mycoplasma pneumoniae.



Figure: **Streptococcal pharyngitis**: A severe case of strep throat or Streptococcal pharyngitis.

Streptococcal pharyngitis, more commonly known as strep throat, is caused by group A beta-hemolytic streptococcus (GAS). This is the most common bacterial cause of pharyngitis (15–30%). Common symptoms of strep throat include fever, sore throat, and large lymph nodes. It is a contagious infection, spread by close contact with an infected individual. A throat culture is the gold standard for the diagnosis of streptococcal pharyngitis, with a sensitivity of 90–95%. A rapid strep test (also called rapid antigen detection testing, or RADT) is also occasionally used as a diagnostic. While the rapid strep test is quicker, it has a lower sensitivity

(70%) and a statistically equal specificity (98%) as a throat culture. For step throat, antibiotics are useful in preventing complications and expediting recovery.

Fusobacterium necrophorum are normal inhabitants of the oropharyngeal flora. Occasionally, however, these bacteria can create a peritonsillar abscess. In 1 out of 400 untreated cases, Lemierre's syndrome can occur as a result of these abscesses.

Diphtheria is a potentially life threatening upper respiratory infection caused by Corynebacterium diphtheriae. As a result of childhood vaccination programs, diphtheria has has been largely eradicated in developed nations, but it is still reported in the Third World, and, increasingly, in some areas in Eastern Europe. Antibiotics are effective in the early stages, but recovery is generally slow.

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15.12B: Scarlet Fever

Learning Objectives

- Describe the bacterium *Streptococcus pyogenes* that causes scarlet fever

A Bacteriophage Hitchhiker

Scarlet fever is an infectious disease which most commonly affects 4-8 year-old children. Symptoms include sore throat, fever, and a characteristic red rash. It is usually spread by inhalation. There is no vaccine, but the disease is effectively treated with antibiotics. Scarlet fever is caused by an erythrogenic toxin, a substance produced by the bacterium Streptococcus pyogenes (group A strep.) when it is infected by a certain bacteriophage.



Figure: **Scarlet Fever**: The rosy cheeks and white area around the mouth are typical symptoms of scarlet fever.

Scarlet fever is caused by secretion of pyrogenic (fever inducing) exotoxins by the infected Streptococcus. Exotoxin A (speA) is probably the best studied of these toxins. It is carried by the bacteriophage T12, which integrates into the Streptococcal genome, from where the toxin is transcribed.

The phage itself integrates into a serine tRNA gene on the chromosome. The T12 virus itself has not been placed into a taxon by the International Committee on Taxonomy of Viruses. It has a double stranded DNA genome; on morphological grounds it appears to be a member of the Siphoviridae. The speA gene was cloned and sequenced in 1986. It is 753 base pairs in length and encodes a 29.244 kiloDalton (kDa) protein. The protein contains a putative 30 amino acid signal peptide. Removal of the signal sequence gives a predicted molecular weight of 25.787 (kDa) for the secreted protein. Both a promoter and a ribosome-binding site (Shine-Dalgarno sequence) are present upstream of the gene. A transcriptional terminator is located 69 bases downstream from the translational termination codon. The carboxy terminal portion of the protein exhibits extensive homology with the carboxy terminus of Staphylococcus aureus enterotoxins B and C1. Streptococcal phages other than T12 may also carry the speA gene.

Key Points

- Scarlet fever usually affects children. Historically, it had devastating effects.
- While antibiotics are effective against scarlet fever, the illness is actually caused by a bacteriophage infecting Streptococcus that has infected a person.
- The bacteriophage T12 inserts into the genome of Streptococcus. This leads to the expression of an exotoxin, which causes scarlet fever.

Key Terms

- **scarlet fever**: a streptococcal infection, mainly occurring among children, and characterized by a red skin rash, sore throat and fever
- **Shine-Dalgarno sequence**: A ribosomal binding site in the mRNA of prokaryotes.
- **exotoxin**: Any toxin secreted by a microorganism into the surrounding environment.
- **enterotoxin**: Any of several toxins produced by intestinal bacteria

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15.12C: Diphtheria

Diphtheria is an upper respiratory infection that is largely benign unless left untreated, at which point very harmful toxins are produced.

Learning Objectives

- Discuss the role of diphtheria toxin in diphtheria

Key Points

- Diptheria is caused bu the bacteria Corynebacterium diphtheriae, and is easily treated with antibiotics. It is now a fairly rare disease in developed countries.
- If left untreated and if infected by a bacteriophage, then Corynebacterium diphtheriae produces toxins that can lead to mortality.
- Diphtheria toxinis comprised of two fragments, fragment A and fragment B;. Fragment B binds to the target cell surface and allows entry into cells through endosomes; fragment A inhibits protein translation.
- Fragment A inhibits protein synthesis by catalyzing EF-2 a protein essential for tRNA movement during protein translation.

Key Terms

- **ribosylation**: The attachment of a ribose or ribosyl group to a molecule, especially to a polypeptide or protein
- **translation**: A process occurring in the ribosome, in which a strand of messenger RNA (mRNA) guides assembly of a sequence of amino acids to make a protein.

Overview of Diphtheria

Diphtheria is an upper respiratory tract illness caused by *Corynebacterium diphtheriae*, a facultative, anaerobic, Gram-positive bacterium. It is characterized by sore throat, low fever, and an adherent membrane (a pseudomembrane) on the tonsils, pharynx, and/or nasal cavity. A milder form of diphtheria can be restricted to the skin. Less common consequences include myocarditis (about 20% of cases) and peripheral neuropathy (about 10% of cases).

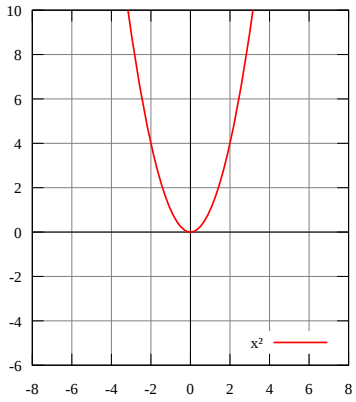

Figure: **Graph of $y=x^2$**

Diphtheria is a contagious disease spread by direct physical contact or breathing the aerosolized secretions of infected individuals. Historically quite common, diphtheria has largely been eradicated in industrialized nations through widespread vaccination. In the United States, for example, there were 52 reported cases of diphtheria between 1980 and 2000; between 2000 and 2007, there were only three cases as the diphtheria–pertussis–tetanus (DPT) vaccine is recommended for all school-age children. Boosters of the vaccine are recommended for adults, since the benefits of the vaccine decrease with age without constant re-exposure; they are particularly recommended for those traveling to areas where the disease has not been eradicated.

Advanced Cases of Diphtheria

In cases that progress beyond a throat infection, diphtheria toxin spreads through the blood and can lead to potentially life-threatening complications that affect other organs, such as the heart and kidneys. The toxin can cause damage to the heart that

affects its ability to pump blood or the kidneys' ability to clear wastes. It can also cause nerve damage, eventually leading to paralysis. About 40% to 50% of those left untreated can die.

Diphtheria toxin is produced by *C. diphtheriae* only when it is infected with a bacteriophage that integrates the toxin-encoding genetic elements into the bacteria. Diphtheria toxin is a single, 60,000 dalton molecular weight protein composed of two peptide chains, fragment A and fragment B, held together by a disulfide bond. Fragment B is a recognition subunit that gains the toxin entry into the host cell by binding to the EGF-like domain of heparin-binding EGF-like growth factor (HB-EGF) on the cell surface. This signals the cell to internalize the toxin within an endosome via receptor-mediated endocytosis. Inside the endosome, the toxin is split by a trypsin-like protease into its individual A and B fragments. The acidity of the endosome causes fragment B to create pores in the endosome membrane, thereby catalyzing the release of fragment A into the cell's cytoplasm.

Fragment A inhibits the synthesis of new proteins in the affected cell. It does this by catalyzing ADP-ribosylation of elongation factor EF-2—a protein that is essential to the translation step of protein synthesis. This ADP-ribosylation involves the transfer of an ADP-ribose from NAD+ to a diphthamide (a modified histidine) residue within the EF-2 protein. Since EF-2 is needed for the moving of tRNA from the A-site to the P-site of the ribosome during protein translation, ADP-ribosylation of EF-2 prevents protein synthesis. ADP-ribosylation of EF-2 is reversed by giving high doses of nicotinamide (a form of vitamin B3), since this is one of the reaction 's end-products, thus high amounts will drive the reaction in the opposite direction counteracting the toxin.



Figure: **Diphtheria toxin induced lesion**: Corynebacterium diphtheriae produces toxins that can affect the skin by causing skin lesions, as shown here.

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15.12D: Otitis Media

Otitis media, or earache, is the inflammation of the middle ear and is often due to bacterial infections.

Learning Objectives

- Discuss the causes and symptoms associated with otitis media

Key Points

- Bacterial-caused earaches are often due to Streptococcus pneumoniae, a common bacterial infection.
- Trimeric Autotransporter Adhesins on the surface of bacteria are the proteins responsible for earaches.
- TAA proteins bind to host cells, allowing the invading bacteria to transfer virulence factors which then cause inflammation of the middle ear.

Key Terms

- **Eustachian tube**: In humans and other land vertebrates, a tube that links the pharynx to the cavity of the middle ear to allow the equalization of the pressure on both sides of the eardrum.
- **tympanic**: relating to the eardrum or middle ear; tympanal

Otitis media is inflammation of the middle ear. It occurs in the area between the tympanic membrane and the inner ear, also effecting a duct known as the eustachian tube. It is one of the two most common causes of earache – the other being otitis externa. Diseases other than ear infections can also cause ear pain, including various cancers of any structure that share nerve supply with the ear. Though painful, otitis media is not threatening and usually heals on its own within 2–6 weeks. Typically, acute otitis media follows a cold. After a few days of a stuffy nose, the ear becomes involved and can cause severe pain. The pain will usually settle within a day or two, but can last over a week. Sometimes the ear drum ruptures, discharging pus from the ear, but the ruptured drum will usually heal rapidly.



Figure: **Acute Otitis Media**: This is a view of the tympanic membrane showing inflammation and redness, typical of acute otitis media.

Otitis media is most commonly caused by infection with viral, bacterial, or fungal pathogens. The most common bacterial pathogen is Streptococcus pneumoniae. Others include Pseudomonas aeruginosa, nontypeable Haemophilus influenzae and Moraxella catarrhalis. Among older adolescents and young adults, the most common cause of ear infections is Haemophilus influenzae. Viruses like respiratory syncytial virus (RSV) and those that cause the common cold may also result in otitis media by damaging the normal defenses of the epithelial cells in the upper respiratory tract. A major risk factor for developing otitis media is Eustachian tube dysfunction, which leads to the ineffective clearing of bacteria from the middle ear.

Otitis media caused by bacterial infections are due to Trimeric Autotransporter Adhesins (TAA; proteins found on the outer membrane of Gram-negative bacteria. Bacteria use TAAs in order to infect their host cells via a process called cell adhesion. TAAs are virulence factors; an infective agent that infects the host cell by attaching to them and secreting the virulence factor by a secretion pathway. The UspA1 protein domain is a TAA found in the bacteria Moraxella catarrhalis, which causes middle ear infections in humans.

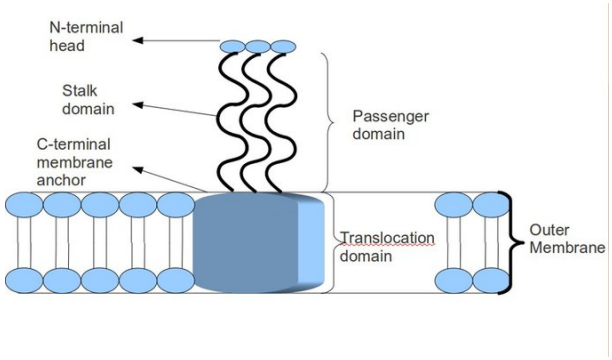

Figure: **Trimeric Autotransporter Adhesin structure**: The structure on the top (outside) of the outer membrane is a TAA protein. Various parts of the TAA are labelled, including the N-terminal head, stalk domain and C-terminal membrane anchor.

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15.12E: Whooping Cough

Pertussis, more commonly known as whooping cough, is a bacterial infection of the upper respiratory system.

Learning Objectives

- Describe the mechanism of action and causes of pertussis causing bacteria

Key Points

- Whooping cough is caused by the bacteria Bordetella pertussis, which infects the respiratory system.
- There is no zoonotic reservoir of Bordetella pertussis, meaning that humans appear to be the only host of this bacteria.
- Bordetella pertussis produces a number of virulence factors, notably Ptx, which inhibits the ability of phagocytes to respond to infections. This helps Bordetella pertussis spread throughout a host.

Key Terms

- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.
- **glottis**: an organ of speech, located in the larynx, and consisting of the true vocal cords and the opening between them
- **lymphocytes**: type of white blood cells in the vertebrate immune system

Pertussis

Pertussis, also known as whooping cough, is an infection of the respiratory system characterized by a “whooping” sound that an afflicted person makes when breathing inwards. Only 50% of patients actually display the classic sound as they attempt to draw breath over a partially closed glottis. In the U.S., the infection was responsible for 5,000 to 10,000 deaths per year before a vaccine was developed and made available. Vaccination has transformed this. Between 1985 and 1988, fewer than 100 children died from pertussis. In 2000, according to the WHO, around 39 million people worldwide were being infected annually. Of these, about 297,000 died.

Causes of Pertussis

Pertussis is caused by the bacteria, Bordetella pertussis, a gram-negative, aerobic coccobacillus capsulate of the genus Bordetella. Bordetella pertussis infects its host by colonizing lung epithelial cells. The bacterium contains a surface protein, filamentous haemagglutinin adhesin, which binds to the sulfatides found on the cilia of epithelial cells. Once anchored, the bacterium produces tracheal cytotoxin, which stops the cilia from beating. This prevents the cilia from clearing debris from an organism ‘s lungs, and the body responds by sending the host into a coughing fit. These coughs expel some bacteria into the air, which are free to infect other hosts. There does not appear to be a zoonotic reservoir for B. pertussis. Humans are its only host. The bacterium is spread by airborne droplets, and its incubation period is one to two weeks.

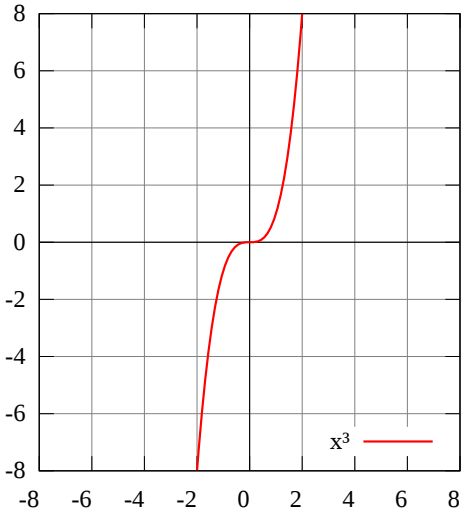

Figure: **Graph of $y=x^3$**

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B. pertussis has the ability to inhibit the function of a host's immune system, through virulence factors. Its virulence factors include pertussis toxin, filamentous hæmagglutinin, pertactin, fimbria, and tracheal cytotoxin. The pertussis toxin, or PTx, inhibits G protein coupling that regulates an adenylate cyclase-mediated conversion of ATP to cyclic AMP. The end result is that phagocytes convert too much ATP to cyclic AMP, which can cause disturbances in cellular signaling mechanisms. This prevents phagocytes from correctly responding to an infection. PTx, formerly known as lymphocytosis -promoting factor, causes a decrease in the entry of lymphocytes into lymph nodes. This can lead to a condition known as lymphocytosis, which is a large increase in the number of lymphocytes in an organism's blood.

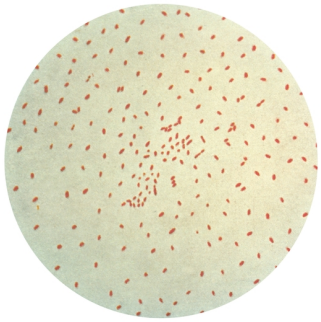

Figure: **Bordetella pertussis**: Bordetella pertussis, the bacteria that causes whooping cough

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15.12F: Tuberculosis

Tuberculosis is a common, and in many cases lethal, infectious bacterial disease that mainly affects the lungs.

Learning Objectives

- Summarize the risk factors associated with tuberculosis (TB)

Key Points

- Tuberculosis is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air.
- The classic symptoms of active TB infection are a chronic cough with blood -tinged sputum, fever, night sweats, and weight loss.
- Diagnosis of active TB relies on radiology (commonly chest x-rays) as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the Mantoux tuberculin skin test.
- Antibiotic resistance is a growing problem in the treatment of tuberculosis.

Key Terms

- **latent**: Existing or present but concealed or inactive.
- **tuberculosis**: An infectious disease of humans and animals caused by a species of mycobacterium mainly infecting the lungs where it causes tubercles characterized by the expectoration of mucus and sputum, fever, weight loss, and chest pain. It is transmitted through inhalation or ingestion of bacteria.
- **pleurisy**: inflammation of lung pleura
- **sputum**: Matter coughed up and expectorated from the mouth, composed of saliva and discharges from the respiratory passages such as mucus, phlegm, or pus.

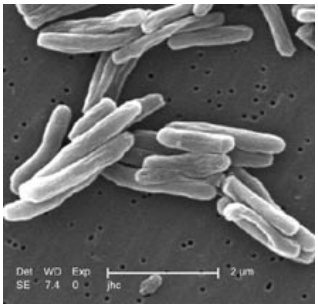

Figure: **Electron micrograph of Mycobacterium tuberculosis.**: This bacteria is primarily responsible for TB.

Tuberculosis (TB; short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis . Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air. Most infections are asymptomatic and latent, but about one in 10 latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those infected. One third of the world's population is thought to have been infected with M. tuberculosis with new infections occurring at a rate of about one per second.

Symptoms

The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, chills night sweats, and weight loss. Tuberculosis may infect any part of the body, but most commonly occurs in the lungs, known as pulmonary tuberculosis. Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, but may co-exist with pulmonary TB as well. Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV this occurs in more than 50% of cases. Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (osseous tuberculosis). Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs.

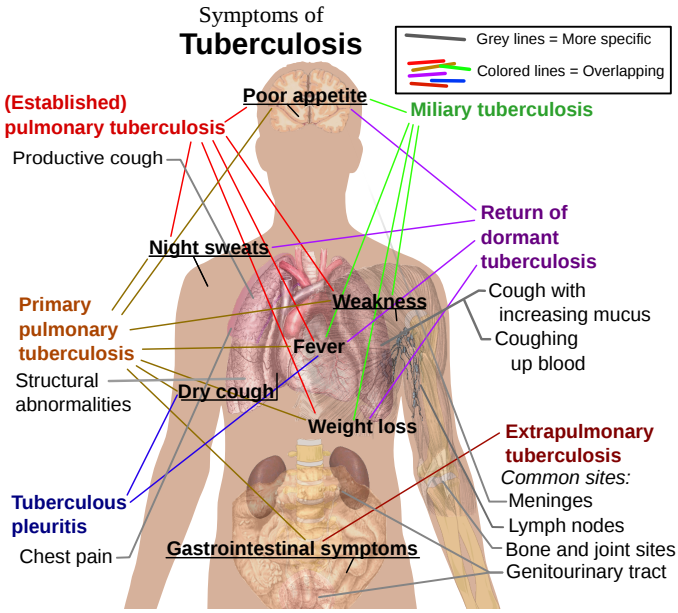

Figure: **Tuberculosis Symptoms.**: Diagram depicting various TB symptoms.

Diagnostics

Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks. A chest x-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation. A definitive diagnosis of TB is made by identifying M. tuberculosis in a clinical sample such as sputum, pus, or a tissue biopsy. However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture.

The Mantoux tuberculin skin test is often used to screen people at high risk for TB. It involves injecting an protein extraction of the tuberculosis bacteria under the skin, and then examining the site 36-48 hours later. A person who has been exposed to the bacteria and has previously formed antibodies is expected to mount an immune response, displaying a raised, red area of skin at the site of injection. The test does have limited accuracy, especially in immunosuppressed people, and is typically used in combination with clinical findings and x-rays to reach a diagnosis.

Risk Factors

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all TB cases are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty. Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather, such as prisons and homeless shelters; medically underprivileged and resource-poor communities; high-risk ethnic minorities, children in close contact with high-risk category patients, and health care providers serving these clients. Chronic lung disease is another significant risk factor. Those who smoke cigarettes have nearly twice the risk of TB than non-smokers. Other disease states can also increase the risk of developing tuberculosis, including alcoholism and diabetes mellitus. Certain medications that cause immunosuppression such as corticosteroids and infliximab, are becoming increasingly important risk factors, especially in the developed world.

Treatment

Treatment of TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective. The two antibiotics commonly used are isoniazid and rifampicin. Treatments can be prolonged, from months to even years. A barrier to effective treatment is patient noncompliance. Due to the long duration of treatment, patients will often forget to take their antibiotics periodically or stop taking them altogether. This contributes to the development of drug-resistant tuberculosis. Many strains of tuberculosis have already become resistant to previous treatments, including a strain that is resistant to all antibiotics.

Latent TB treatment usually employs a single antibiotic, while active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance. People with latent infections are also treated to prevent them from progressing to active TB disease later in life.

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15.12G: Bacterial Pneumonias

Pneumonia is an inflammatory lung disease that can lead to problems with breathing, often caused by bacterial infections.

Learning Objectives

- List the various causes of bacterial pneumonia

Key Points

- Most cases of pneumonia are caused by bacterial infections, and most of the bacterial infections are caused by the bacteria Streptococcus pneumoniae.
- The bacteria that cause pneumonia are split into three groups, gram-negative, gram-positive and atypical.
- Alcoholism is asociated with Streptococcus pneumoniae induced pneumonia and smoking exacerbates the situation.

Key Terms

- **pneumonia**: Pneumonia is an inflammatory condition of the lung, affecting primarily the microscopic air sacs known as alveoli.
- **infection**: An uncontrolled growth of harmful microorganisms in a host.
- **Alveoli**: alveolus (plural alveoli) a small air sac in the lungs, where oxygen and carbon dioxide are exchanged with the blood.

Pneumonia is an inflammatory condition of the lung, affecting primarily the microscopic air sacs known as alveoli. It is usually caused by infection with viruses or bacteria and less commonly other microorganisms, certain drugs and other conditions such as autoimmune diseases. Typical symptoms include a cough, chest pain, fever, and difficulty breathing. Diagnostic tools include x-rays and culture of the sputum. Vaccines to prevent certain types of pneumonia are available. Treatment depends on the underlying cause. Presumed bacterial pneumonia is treated with antibiotics. If the pneumonia is severe, the affected person is generally admitted to hospital.

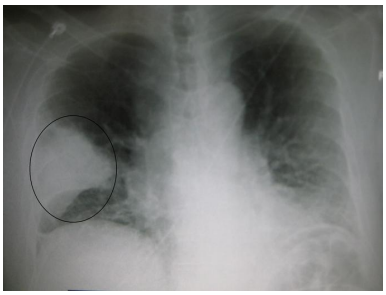

Figure: **Bacterial pneumonia**: A chest X-ray showing a very prominent wedge-shaped bacterial pneumonia in the right lung.

Bacteria are the most common cause of community-acquired pneumonia (CAP), with Streptococcus pneumoniae isolated in nearly 50% of cases. Other commonly isolated bacteria include: Haemophilus influenzae in 20%, Chlamydophila pneumoniae in 13%, and Mycoplasma pneumoniae in 3% of cases; Staphylococcus aureus; Moraxella catarrhalis; Legionella pneumophila and Gram-negative bacilli. A number of drug-resistant versions of the above infections are becoming more common, including drug-resistant Streptococcus pneumoniae (DRSP) and methicillin-resistant Staphylococcus aureus (MRSA). The spreading of organisms is facilitated when risk factors are present. Alcoholism is associated with Streptococcus pneumoniae, anaerobic organisms and Mycobacterium tuberculosis; smoking facilitates the effects of Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Legionella pneumophila. Exposure to birds is associated with Chlamydia psittaci; farm animals with Coxiella burnetti; aspiration of stomach contents with anaerobic organisms; and cystic fibrosis with Pseudomonas aeruginosa and Staphylococcus aureus. Streptococcus pneumoniae is more common in the winter, and should be suspected in persons who aspirate a large amount anaerobic organisms.

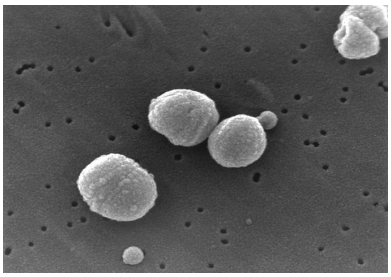

Figure: **Streptococcus pneumoniae**: The bacterium Streptococcus pneumoniae, a common cause of pneumonia, imaged by an electron microscope

Bacteria caused pneumonia fall into 3 groups:

1. Gram Positive. Streptococcus pneumoniae is the most common bacterial cause of pneumonia in all age groups except newborn infants. Streptococcus pneumoniae is a Gram-positive bacterium that often lives in the throat of people who do not have pneumonia. Other important Gram-positive causes of pneumonia are Staphylococcus aureus and Bacillus anthracis.
2. Gram Negative. Gram-negative bacteria are seen less frequently: Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, and Moraxella catarrhalis are the most common. These bacteria often live in the gut and enter the lungs when contents of the gut (such as vomit or faeces) are inhaled.
3. Atypical bacteria. “Atypical” bacteria are Coxiella burnetii, Chlamydophila pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila. Many people falsely believe they are called “atypical” because they are uncommon and/or do not respond to common antibiotics and/or cause atypical symptoms. In reality, they are “atypical” because they do not gram stain as well as gram-negative and gram-positive organisms. Pneumonia caused by Yersinia pestis is usually called pneumonic plague.

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SECTION OVERVIEW

15.13: Viral Diseases of the Respiratory System

Topic hierarchy

15.13A: Colds

15.13B: Viral Pneumonia

15.13C: Respiratory Syncytial Virus Infection

15.13D: Coryza and Influenza

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15.13A: Colds

The common cold is caused by several different viruses and is the most common human viral infection.

Learning Objectives

- Recognize the major viruses known to cause the common cold: rhinovirus, human parainfluenza virus and the human respiratory syncytial virus (RSV)

Key Points

- Over 200 virus types have been found that cause the common cold, with rhinoviruses being the most common.
- Rhinoviruses are a sub-type of picornavirus, a non-enveloped RNA virus, which is very small in size.
- The symptoms of the common cold are not due to the viral infection directly but rather the bodies response to the virus.
- There is no cure for the common cold, and in fact antibiotics which often prescribed are detrimental to patients.

Key Terms

- **serotypes**: A group of microorganisms characterized by a specific set of antigens; serovar.
- **capsid**: The outer protein shell of a virus.

The common cold (also known as nasopharyngitis, rhinopharyngitis, acute coryza, or a cold) is a viral infectious disease of the upper respiratory tract which affects primarily the nose. Symptoms include coughing, sore throat, runny nose, and fever which usually resolve in seven to ten days, with some symptoms lasting up to three weeks. Well over 200 viruses are implicated in the cause of the common cold. The most commonly implicated virus is a rhinovirus (30–80%), a type of picornavirus with 99 known serotypes. A picornavirus is a virus belonging to the family Picornaviridae. Picornaviruses are non-enveloped RNA viruses with an icosahedral capsid. The name is derived from pico, meaning small, and RNA, referring to the ribonucleic acid genome, so "picornavirus" literally means small RNA virus. Others include: coronavirus (10–15%), human parainfluenza viruses, human respiratory syncytial virus, adenoviruses, enteroviruses, and metapneumovirus. Frequently more than one virus is present.

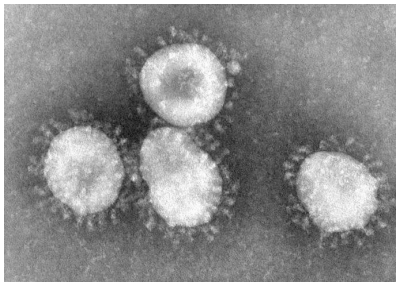

Figure: **Coronaviruses**: Coronaviruses are a group of viruses that have a halo, or crown-like (corona) appearance when viewed under an electron microscope. If you have a cold 10-15% of the time it is caused by a virus like this.

The symptoms of the common cold are believed to be primarily related to the immune response to the virus. The mechanism of this immune response is virus specific. For example, the rhinovirus is typically acquired by direct contact; it binds to human ICAM-1 receptors through unknown mechanisms to trigger the release of inflammatory mediators. These inflammatory mediators then produce the symptoms. It does not generally cause damage to the nasal epithelium. The respiratory syncytial virus (RSV) on the other hand is contracted by both direct contact and air born droplets. It then replicates in the nose and throat before frequently spreading to the lower respiratory tract. RSV does cause epithelium damage. Human parainfluenza virus typically results in inflammation of the nose, throat, and bronchi. In young children when it affects the trachea it may produce the symptoms of croup due to the small size of their airway.

No cure for the common cold exists, but the symptoms can be treated. Antibiotics have no effect against viral infections and thus have no effect against the viruses that cause the common cold. Due to their side effects they cause overall harm; however, they are still frequently prescribed.It is the most frequent infectious disease in humans with the average adult contracting two to three colds a year and the average child contracting between six and twelve. These infections have been with humanity since antiquity.

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15.13B: Viral Pneumonia

Viral pneumonia, one of the two leading causes of pneumonia, more commonly affects children.

Learning Objectives

- Outline the route of infection for a virus that causes pneumonia

Key Points

- Viral pneumonia is caused by both viral infection which leads to cell death. The body's response to clear the cellular debris leads to further inflammation and the blockage of respiration.
- Many different viruses can cause viral pneumonia, but they all enter the lungs and damage the alveoli.
- The best prevention for viral pneumonia is to vaccinate against the viruses that can cause pneumonia.

Key Terms

- **Alveoli**: alveolus (plural alveoli) a small air sac in the lungs, where oxygen and carbon dioxide are exchanged with the blood.
- **cytokines**: Regulatory proteins that function in the regulation of the cells involved in immune system function
- **apoptosis**: The process of programmed cell death by which cells undergo an ordered sequence of events which lead to death of the cell. This occurs during growth and development of the organism, as a part of normal cell aging, or as a response to cellular injury.

Pneumonia is an inflammatory condition of the lung that particularly affects microscopic air sacs (alveoli). It is associated with fever and chest symptoms, and it appears as a lack of space on a chest x-ray. The inflammation may be caused by infection from viruses, bacteria, or other microorganisms. Less commonly, it is caused by certain drugs and other conditions. Viruses and bacteria are the two leading causes of pneumonia, while fungi and parasites are less common. Viruses are the most common cause of pneumonia in children, while bacteria are the most common cause in adults.

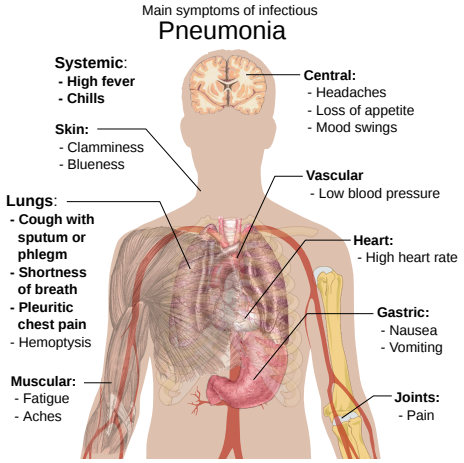

Figure: **Symptoms of pneumonia**: Typical symptoms associated with pneumonia.

How Viruses Cause Pneumonia

Many types of viral infections can cause pneumonia, but in order to do this, these viruses must first invade cells in order to reproduce. Typically, a virus will reach the lungs by traveling in droplets through the mouth and nose during inhalation. Once there, the virus will invade the cells that line the airways and the alveoli. This invasion often leads to cell death, in which either the virus directly kills the cell, or the cell self-destructs through apoptosis. Further damage to the lungs occurs when the immune system responds to the infection. White blood cells, in particular lymphocytes, are responsible for activating a variety of chemicals (cytokines) which cause fluid to leak into the alveoli. The combination of cellular destruction and fluid-filled alveoli interrupts the transportation of oxygen into the bloodstream. Thus, in large part, as with other viral infections, it is the body's response to the virus that causes the symptoms of pneumonia, and not necessarily the viral infection itself. In addition to their effects on the lungs, many viruses affect other organs and can lead to illnesses that affect other bodily functions. Viruses also make the body more susceptible to bacterial infection. For this reason, bacterial pneumonia often complicates viral pneumonia.

Which Viruses Cause Pneumonia

Common viruses that cause pneumonia include influenza viruses A and B, respiratory syncytial viruses (RSV), and human parainfluenza viruses (hPIV), the last of which particularly affects children. Rarer viruses that commonly cause pneumonia include adenoviruses (in military recruits), metapneumoviruses, and severe acute respiratory syndrome virus (SARS coronavirus). Viruses that primarily cause other diseases, but sometimes cause pneumonia, include herpes simplex virus (HSV, mainly in newborns), varicella- zoster virus (VZV), measles virus, rubella virus, and cytomegalovirus (CMV, mainly in people with immune system problems). In children with pneumonia, the most commonly identified agents are respiratory syncytial virus, rhinovirus, human metapneumovirus, human bocavirus, and parainfluenza viruses. Because of this, the best prevention against viral pneumonia is vaccination against influenza, adenovirus, chickenpox, herpes zoster, measles, and rubella.

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15.13C: Respiratory Syncytial Virus Infection

Human respiratory syncytial virus (RSV) causes respiratory tract infections in humans.

Learning Objectives

- Recognize the traits associated with the human respiratory syncytial virus (RSV) and its mode of infection

Key Points

- RSV is a single stranded virus, the genome of which encodes 11 proteins which play different roles in RSV infection.
- RSV can induce syncytia (aggregates of host cells), providing further fertile ground for RSV to propagate.
- There is no direct treatment of RSV except to mitigate the symptoms, giving the patient's body time to fight off the infection.

Key Terms

- **cannula**: A hose or tube that connects directly to an oxygen (O2) bottle/source from the user's nose, commonly used by aircraft pilots or others needing a direct oxygen breathing apparatus.
- **prophylactic**: A medicine that preserves or defends against disease; a preventive.
- **hypertonic**: Having a greater osmotic pressure than another.

Respiratory Syncytial Virus Infection

Human respiratory syncytial virus (RSV) is a virus that causes respiratory tract infections. It is a major cause of lower respiratory tract infections and hospital visits during infancy and childhood. A prophylactic medication (not a vaccine) exists for preterm-birth (under 35 weeks gestation) infants, and for infants with a congenital heart defect or bronchopulmonary dysplasia. Of those infected with RSV, 2–3% will develop bronchiolitis, necessitating hospitalization.

RSV is a negative-sense, single-stranded RNA virus of the family Paramyxoviridae, which includes common respiratory viruses such as those causing measles and mumps. RSV is a member of the paramyxovirus subfamily Pneumovirinae. RSV has ten genes encoding 11 proteins. There are two open reading frames of M2. NS1 and NS2 inhibit type I interferon activity. N encodes the nucleocapsid protein that associates with the genomic RNA forming the nucleocapsid. M encodes the matrix protein required for viral assembly. SH, G and F form the viral coat. The G protein is a surface protein; it functions as the attachment protein, the protein which attaches the virus to target cells. The F protein is another important surface protein. RSV's name comes from the fact that F proteins on the surface of the virus cause the cell membranes on nearby cells to merge, forming syncytia.

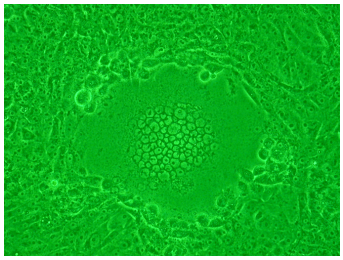

Figure: **Syncytium**: The mass or "ball" of cells in the middle of the image are a syncytium of cells that formed due to infection by the HIV virus.

Syncytia are aggregates of cells that can form when cells are infected with certain types of viruses, notably HIV and paramyxoviruses such as RSV. During infection, viral fusion proteins used by the virus to enter the cell are transported to the cell surface where they can cause the host cell membrane to fuse with neighboring cells. This presumably works to the virus's advantage, as aggregates of target cells provide more hosts for the virus to infect and multiply. F proteins also mediate viral fusion, allowing entry of the virus into the cell cytoplasm and also allowing the formation of syncytia. Antibodies directed at the F protein are neutralizing. M2 is the second matrix protein required for viral transcription; it encodes M2-1 (elongation factor) and M2-2 (transcription regulation), while L encodes the RNA polymerase. The phosphoprotein P is a cofactor for L. The genome is transcribed sequentially from NS1 to L with reduction in expression levels along its length.

Treatment of RSV is limited to supportive care, including oxygen therapy. Studies of nebulized hypertonic saline (HS) have shown that the "use of nebulized 3% HS is a safe, inexpensive, and effective treatment for infants hospitalized with moderately severe viral bronchiolitis" where "RSV accounts for the majority of viral bronchiolitis cases. " Supportive care includes fluids and oxygen

until the illness runs its course. Increased airflow, humidified and delivered via nasal cannula, may be supplied in order to reduce the effort required for respiration.

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15.13D: Coryza and Influenza

Influenza is an infectious disease caused by RNA viruses of the family Orthomyxoviridae that affects birds and mammals.

Learning Objectives

- Differentiate between the respiratory system disorders of influenza and coryza

Key Points

- The most common symptoms of the disease are chills, fever, sore throat, muscle pains, severe headache, coughing, weakness/fatigue, and general discomfort.
- Influenza is transmitted through the air by coughs or sneezes, by direct contact with bird droppings or nasal secretions, or through contact with contaminated surfaces.
- Coryza is a word describing the symptoms of a cold and refers to the inflammation of the mucous membranes lining the nasal cavity which usually gives rise to the symptoms of congestion.

Key Terms

- **coryza**: Inflammation of the mucous membranes lining the nasal cavity, usually causing a running nose, nasal congestion, and loss of smell.
- **RNA virus**: Any of many viruses that possess ribonucleic acid as their genetic material and do not replicate using DNA.
- **influenza**: An acute contagious disease of the upper airways and lungs, caused by a virus, which rapidly spreads around the world in seasonal epidemics.

Influenza, commonly referred to as the flu, is an infectious disease caused by RNA viruses of the family Orthomyxoviridae that affects birds and mammals. The most common symptoms of the disease are chills, fever, sore throat, muscle pains, severe headache, coughing, weakness/fatigue, and general discomfort. Although it is often confused with other influenza-like illnesses, especially the common cold, influenza is a more severe disease than the common cold. The general symptoms of influenza are summarized in.

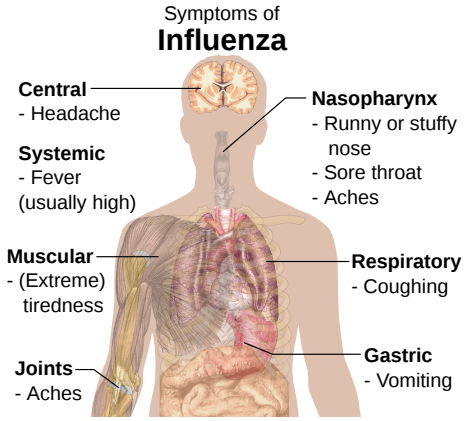

Figure: **Symptoms of influenza**: Symptoms of influenza with fever and cough the most common symptoms.

Typically, influenza is transmitted through the air by coughs or sneezes, creating aerosols containing the virus. Influenza can also be transmitted by direct contact with bird droppings or nasal secretions, or through contact with contaminated surfaces. Reasonably effective ways to reduce the transmission of influenza include good personal health and hygiene habits such as: not touching your eyes, nose or mouth; frequent hand washing, covering coughs and sneezes, avoiding close contact with sick people and staying home yourself if you are sick.

Vaccinations against influenza are usually made available to people in developed countries. The most common human vaccine is the trivalent influenza vaccine (TIV) that contains purified and inactivated antigens against three viral strains. Typically, this vaccine includes material from two influenza A virus subtypes and one influenza B virus strain. The TIV carries no risk of transmitting the disease, and it has very low reactivity. A vaccine formulated for one year may be ineffective in the following year, since the influenza virus evolves rapidly, and new strains quickly replace the older ones.

Influenza viruses A, B, and C are very similar in overall structure and a diagram of the structure of the virus can be seen in Figure 2. The viral particles of all influenza viruses are similar in composition. They are made of a viral envelope containing two main types of glycoproteins, wrapped around a central core. The central core contains the viral RNA genome and other viral proteins that package and protect this RNA. RNA tends to be single stranded, but in special cases it is double. Unusually for a virus, its genome is not a single piece of nucleic acid but seven or eight pieces of segmented negative-sense RNA. Each piece of RNA contain either one or two genes, which code for a gene product (protein). Hemagglutinin (HA) and neuraminidase (NA) are the two large glycoproteins on the outside of the viral particles. HA is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell, while NA is involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles. Furthermore, they are antigens to which antibodies can be raised. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. These different types of HA and NA form the basis of the H and N distinctions in, for example, H5N1. There are 16 H and 9 N subtypes known, but only H 1, 2, and 3, and N 1 and 2 are commonly found in humans.

Antiviral medication can be effective, but some strains of influenza can show resistance to the standard antiviral drugs. The two classes of antiviral drugs used against influenza are neuraminidase inhibitors and M2 protein inhibitors (adamantane derivatives). Neuraminidase inhibitors are currently preferred for flu virus infections since they are less toxic and more effective.

Coryza is a word describing the symptoms of a “cold. ” It describes the inflammation of the mucous membranes lining the nasal cavity which usually gives rise to the symptoms of nasal congestion and loss of smell, among other symptoms. Coryza may not always have an infectious or allergenic etiology and can be due to something as innocuous as a cold wind, spicy food, or tender points in the muscles of the neck such as the sternocleidomastoid. It is also a symptom of narcotic withdrawal. Coryza is classically used in association with the “four Cs” of measles infection: cough, conjunctivitis, Koplik’s spots, and coryza.

Treatment of coryza depends on etiology. Coryza from any allergic causes usually gets relieved if contact with the allergen (dust, pollen, cold wind, etc.) is avoided. Nasal sprays, antihistamines, and decongestants are beneficial. However, if it is due to any virus it usually takes three to seven days to improve.

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SECTION OVERVIEW

15.14: Fungal Diseases of the Respiratory System

Topic hierarchy

15.14A: Histoplasmosis

15.14B: Coccidiomycosis

15.14C: Pneumocystis Pneumonia

15.14D: Blastomycosis

15.14E: Other Fungi Involved in Respiratory Disease

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15.14A: Histoplasmosis

Histoplasmosis is a disease caused by the fungus Histoplasma capsulatum.

Learning Objectives

- Describe the traits associated with and mode of transmission for Histoplasma capsulatum

Key Points

- Histoplasmosis is s a disease caused by the fungus Histoplasma capsulatum, which is usually found in soil, and often associated with decaying bat guano or bird droppings.
- Cases of histoplasmosis have declined acutely since the Industrial Revolution as quality of life improved dramatically and humans were no longer living in their own squalor.
- Symptoms of this infection vary greatly, but the disease affects primarily the lungs. Occasionally, other organs are affected, and it can be fatal if left untreated.

Key Terms

- **Histoplasmosis**: Histoplasmosis is a disease caused by the fungus Histoplasma capsulatum. Symptoms of this infection vary greatly, but the disease primarily affects the lungs. Other organs are occassionally affected; this is called disseminated histoplasmosis and can be fatal if left untreated.
- **fungus**: Any member of the kingdom Fungi; a eukaryotic organism typically having chitin cell walls but no chlorophyll or plastids. Fungi may be unicellular or multicellular.

Histoplasmosis (also known as “Cave disease,” “Darling’s disease,” “Ohio valley disease,” “Reticuloendotheliosis,” “Spelunker’s Lung,” and “Caver’s disease”) is a disease caused by the fungus Histoplasma capsulatum. Symptoms of this infection vary greatly, but the disease primarily affects the lungs. Other organs are occasionally affected; this is called disseminated histoplasmosis and can be fatal if left untreated. Histoplasmosis is common among AIDS patients due to their suppressed immune system.

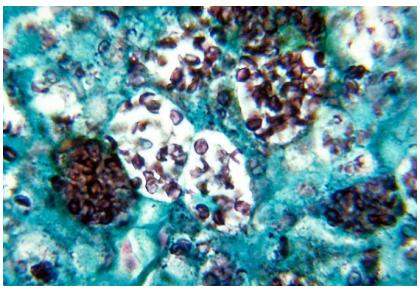

Figure: **Histoplasmosis**: This is a Methenamine silver strain of Histoplasma capsulatum that shows histopathologic changes in the histoplasmosis.

If symptoms of histoplasmosis infection occur, they will start within 3 to 17 days after exposure, with the average being 12 to 14 days. Most affected individuals have clinically silent manifestations and show no apparent ill effects. The acute phase of histoplasmosis is characterized by non-specific respiratory symptoms, often cough or flu-like. Chest X-ray findings are normal in 40 to 70% of cases. Chronic histoplasmosis cases can resemble tuberculosis, and disseminated histoplasmosis affects multiple organ systems and is fatal unless treated.



Figure: **Acute pulmonary histoplasmosis**: This is a chest X-ray of a patient with acute pulmonary histoplasmosis.

Histoplasmosis may be divided into the following types: primary pulmonary histoplasmosis, progressive disseminated histoplasmosis, primary cutaneous histoplasmosis, and African histoplasmosis.

Histoplasma capsulatum is found throughout the world. It is endemic in certain areas of the United States, particularly in states bordering the Ohio River valley and the lower Mississippi River. It is also common in caves in southern and East Africa. Positive histoplasmin skin tests occur in as many as 90% of the people living in areas where Histoplasma capsulatum is common, such as the eastern and central United States.

Histoplasma capsulatum grows in soil and material contaminated with bird or bat droppings (guano). The fungus has been found in poultry house litter, caves, areas harboring bats, and in bird roosts (particularly those of starlings). The fungus is thermally dimorphic: in the environment it grows as a brownish mycelium, and at body temperature (37 °C in humans) it morphs into a yeast. The inoculum is represented principally by microconidia that, once inhaled into the alveolar spaces, germinate and then transform into budding yeast cells. Histoplasmosis is not contagious, but is contracted by inhalation of the spores from disturbed soil or guano.

Histoplasmosis can be diagnosed by samples containing the fungusken from sputum, blood, or infected organs. It can also be diagnosed by detection of antigens in blood or urine samples by ELISA or PCR. It can also be diagnosed by a test for antibodies against Histoplasma in the blood. Histoplasma skin tests indicate whether a person has been exposed, but do not indicate whether they have the disease. Formal histoplasmosis diagnoses are often confirmed only by culturing the fungus directly. Cutaneous manifestations of disseminated disease are diverse and often present as a nondescript rash with systemic complaints. Diagnosis is best established by urine antigen testing. Blood cultures may take up to 6 weeks for diagnostic growth to occur and serum antigen testing often comes back with a false negative before 4 weeks of disseminated infection.

It is not practical to test or decontaminate most sites that may be contaminated with Histoplasma capsulatum, so precautions to reduce a person's risk of exposure are important. Precautions common to all geographical locations would be to avoid accumulations of bird or bat droppings.

Antifungal medications are used to treat severe cases of acute histoplasmosis and all cases of chronic and disseminated disease. Typical treatment of severe disease first involves treatment with amphotericin B, followed by oral itraconazole. Treatment with itraconazole will need to continue for at least a year in severe cases.

In many milder cases, oral itraconazole or ketoconazole is sufficient. Asymptomatic disease is typically not treated. Past infection results in partial protection against ill effects if reinfected.

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15.14B: Coccidiomycosis

Coccidioidomycosis is a fungal disease caused by *Coccidioides immitis* or *C. posadasii*.

Learning Objectives

- Describe the mode of transmission, symptoms and diagnostic test associated with Coccidioidomycosis immitis

Key Points

- C. immitis resides in the soil in certain parts of the southwestern United States, northern Mexico, and parts of Central and South America.
- Infection is caused by inhalation of the particles.
- The disease is usually mild, with flu-like symptoms and rashes.

Key Terms

- **Coccidioidomycosis**: Coccidioidomycosis is a fungal disease caused by Coccidioides immitis or C. posadasii. It is endemic in certain parts of Arizona, California, Nevada, New Mexico, Texas, Utah and northwestern Mexico.
- **fungal**: Of or pertaining to a fungus or fungi
- **inhalation**: The substance (medicament) which is inhaled.

Coccidioidomycosis (commonly known as "Valley fever", as well as "California fever", "Desert rheumatism", and "San Joaquin Valley fever") is a fungal disease caused by *Coccidioides immitis* or *C. posadasii*. It is endemic in certain parts of Arizona, California, Nevada, New Mexico, Texas, Utah and northwestern Mexico.



Figure: **Coccidioidomycosis**: Histopathological changes in a case of coccidioidomycosis of the lung showing a large fibrocaseous nodule.

C. immitis resides in the soil in certain parts of the southwestern United States, northern Mexico, and parts of Central and South America. It is dormant during long dry spells, then develops as a mold with long filaments that break off into airborne spores when the rains come. The spores, known as arthroconidia, are swept into the air by disruption of the soil, such as occurs during construction, farming, or an earthquake.

Infection is caused by inhalation of the particles. The disease is not transmitted from person to person. The infection ordinarily resolves leaving the patient with a specific immunity to re-infection. *C. immitis* is a dimorphic saprophytic organism that grows as a mycelium in the soil and produces a spherule form in the host organism.

The disease is usually mild, with flu-like symptoms and rashes. The Mayo Clinic estimates that half the population in some affected areas have suffered from the disease. On occasion, those particularly susceptible may develop a serious or even fatal illness. Serious complications include severe pneumonia, lung nodules, and disseminated disease, where the fungus spreads throughout the body. The disseminated form of Valley Fever can devastate the body, causing skin ulcers, abscesses, bone lesions, severe joint pain, heart inflammation, urinary tract problems, meningitis, and often death. In order of decreasing risk, people of Filipino, African, Native American, Hispanic, and Asian descent are susceptible to the disseminated form of the disease. Men and pregnant women, and people with weakened immune systems (such as from AIDS), are more susceptible than non-pregnant women.

It has been known to infect humans, cattle, deer, dogs, elk, fish, mules, livestock, apes, kangaroos, wallabies, tigers, bears, badgers, otters and marine mammals.

Symptomatic infection (40% of cases) usually presents as an influenza-like illness with fever, cough, headaches, rash, and myalgia (muscle pain). Some patients fail to recover and develop chronic pulmonary infection or widespread disseminated infection

(affecting meninges, soft tissues, joints, and bone). Severe pulmonary disease may develop in HIV-infected persons.

An additional risk is that health care providers who are unfamiliar with it or are unaware that the patient has been exposed to it may misdiagnose it as cancer and subject the patient to unnecessary surgery.

Coccidioidomycosis may be divided into the following types: Primary pulmonary coccidioidomycosis; Disseminated coccidioidomycosis; and Primary cutaneous coccidioidomycosis.

The fungal infection can be demonstrated by microscopic detection of diagnostic cells in body fluids, exudates, sputum and biopsy-tissue. With specific nucleotide primers, *C.immitis* DNA can be amplified by PCR. It can also be detected in cultures by morphological identification, or by using molecular probes that hybridize with *C.immitis* RNA. An indirect demonstration of fungal infection can be achieved also by serologic analysis detecting fungal antigen or host antibody produced against the fungus.

There are no published prospective studies that examine optimal antifungal therapy for coccidioidomycosis. Mild cases often do not require treatment. Oral Fluconazole and intravenous Amphotericin B are used in progressive or disseminated disease, or in which patients are immunocompromised. Alternatively, itraconazole or ketoconazole may be used. Posaconazole and voriconazole have also been used. There is currently no practical preventative measures available for people who live or travel through Valley Fever endemic areas. It is recommended to avoid airborne dust or dirt, though this is not a guaranteed manner of prevention. People in certain occupations may be advised to wear face masks.

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15.14C: Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) or pneumocystosis is a form of pneumonia, caused by the yeast-like fungus Pneumocystis jirovecii.

Learning Objectives

- Review the symptoms associated with pneumocystis pneumonia and the methods of diagnosis

Key Points

- Pneumocystis jirovecii is a pathogen that is specific to humans.
- Pneumocystis is commonly found in the lungs of healthy people, but, being a source of opportunistic infection, it can cause a lung infection in people with a weak immune system.
- Symptoms of PCP include fever, non-productive cough, shortness of breath, weight loss, and night sweats.

Key Terms

- **Pneumocystis pneumonia**: Pneumocystis pneumonia (PCP) or pneumocystosis is a form of pneumonia, caused by the yeast-like fungus Pneumocystis jirovecii. This pathogen is specific to humans; it has not been shown to infect other animals.
- **Opportunistic**: An opportunistic infection is an infection caused by pathogens, particularly opportunistic pathogens—those that take advantage of certain situations—such as bacterial, viral, fungal or protozoan infections that usually do not cause disease in a healthy host, one with a healthy immune system. A compromised immune system, however, presents an "opportunity" for the pathogen to infect.
- **Symptoms**: A symptom is a departure from normal function or feeling which is noticed by a patient, indicating the presence of disease or abnormality. A symptom is subjective, observed by the patient, and cannot be measured directly.

Pneumocystis pneumonia (PCP) or pneumocystosis is a form of pneumonia, caused by the yeast-like fungus (which had previously been erroneously classified as a protozoan) Pneumocystis jirovecii. This pathogen is specific to humans; it has not been shown to infect other animals. Other species of Pneumocystis that parasitize other animals have not been shown to infect humans.

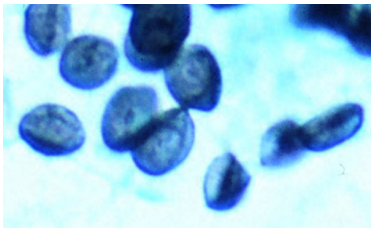

Figure: **Pneumocystis jirovecii pneumonia**: Pneumocystis jirovecii cysts from bronchoalveolar lavage, stained with Toluidin blue O stain

Pneumocystis is commonly found in the lungs of healthy people, but being a source of opportunistic infection, it can cause a lung infection in people with a weak immune system. Pneumocystis pneumonia is especially seen in people with cancer, HIV/AIDS and the use of medications that affect the immune system.

Nomenclature of Pneumocystis Pneumonia

The older name Pneumocystis carinii (which now only applies to the Pneumocystis species that is found in rats), is still in common usage. As a result, Pneumocystis pneumonia (PCP) is also known as Pneumocystis jiroveci[i] pneumonia and (incorrectly) as Pneumocystis carinii pneumonia.

Regarding nomenclature, when the name of Pneumocystis pneumonia changed from P. carinii pneumonia to P. jirovecii pneumonia, it was at first felt that it could no longer be referred to as "PCP". However, because the term PCP was already in common usage, it was rationalized that the term PCP could continue to be used, as it stood for PneumoCystis (jirovecii) Pneumonia.

Symptoms of Pneumocystis Pneumonia

Symptoms of PCP include fever, non-productive cough (because sputum is too viscous to become productive), shortness of breath (especially on exertion), weight loss, and night sweats. There is usually not a large amount of sputum with PCP unless the patient

has an additional bacterial infection. The fungus can invade other visceral organs (such as the liver, spleen, and kidney), but only in a minority of cases.

Pneumothorax is a well-known complication of PCP. An acute history of chest pain with breathlessness and diminished breath sounds is typical of pneumothorax.

The risk of pneumonia due to Pneumocystis jirovecii increases when CD4 positive cell levels are less than 200 cells/µl. In these immunosuppressed individuals the manifestations of the infection are highly variable. The disease attacks the interstitial, fibrous tissue of the lungs, with marked thickening of the alveolar septa and alveoli, leading to significant hypoxia which can be fatal if not treated aggressively. In this situation LDH levels increase and gas exchange is compromised. Oxygen is less able to diffuse into the blood, leading to hypoxia. Hypoxia, along with high arterial carbon dioxide (CO_2) levels, stimulates hyper-ventilatory effort, thereby causing dyspnea (breathlessness).

Diagnosis and Treatment of Pneumocystis Pneumonia

The diagnosis can be confirmed by the characteristic appearance of the chest x-ray, which shows widespread pulmonary infiltrates, and an arterial oxygen level (PaO2) that is strikingly lower than would be expected from symptoms. Gallium 67 scans are also use in the diagnosis. They are abnormal in approximately 90% of cases and are often positive before the chest x-ray becomes abnormal. The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or bronchio-alveolar lavage (lung rinse). Staining with toluidine blue, silver stain, periodic-acid schiff stain, or an immunofluorescence assay will show the characteristic cysts. The cysts resemble crushed ping-pong balls and are present in aggregates of 2 to 8 (and not to be confused with Histoplasma or Cryptococcus, which typically do not form aggregates of spores or cells). A lung biopsy would show thickened alveolar septa with fluffy eosinophilic exudate in the alveoli. Both the thickened septa and the fluffy exudate contribute to dysfunctional diffusion capacity which is characteristic of this pneumonia.

Pneumocystis infection can also be diagnosed by immunofluorescent or histochemical staining of the specimen, and more recently by molecular analysis of polymerase chain reaction products comparing DNA samples. Notably, simple molecular detection of Pneumocystis jirovecii in lung fluids does not mean that a person has Pneumocystis pneumonia or infection by HIV. The fungus appears to be present in healthy individuals in the general population.

Antipneumocystic medication is used with concomitant steroids in order to avoid inflammation, which causes an exacerbation of symptoms about four days after treatment begins if steroids are not used. By far the most commonly used medication is trimethoprim-sulfamethoxazole, but some patients are unable to tolerate this treatment due to allergies. Other medications that are used, alone or in combination, include pentamidine, trimetrexate, dapsone, atovaquone, primaquine, pafuramidine maleate (under investigation), and clindamycin. Treatment is usually for a period of about 21 days. However, pneumocystis pneumonia can be prevented by the drug TMP-SMX.

Pentamidine is less often used as its major limitation is the high frequency of side effects. These include acute pancreatitis, renal failure, hepatotoxicity, leukopenia, rash, fever, and hypoglycemia.

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15.14D: Blastomycosis

Blastomycosis is a fungal infection caused by the organism Blastomyces dermatitidis.

Learning Objectives

- Describe the causes and symptoms of blastomycosis

Key Points

- Infection occurs by inhalation of the fungus from its natural soil habitat.
- Once suspected, the diagnosis of blastomycosis can usually be confirmed by demonstration of the characteristic, broad-based budding organisms in sputum or tissues by KOH prep, cytology, or histology.
- Once inhaled in the lungs, Blastomycosis multiply and may disseminate through the blood and lymphatics to other organs, including the skin, bone, genitourinary tract, and brain.

Key Terms

- **fungal**: Of or pertaining to a fungus or fungi
- **Blastomycosis**: Blastomycosis is a fungal infection caused by the organism Blastomyces dermatitidis. Endemic to portions of North America, blastomycosis causes clinical symptoms similar to histoplasmosis.
- **inhalation**: The substance (medicament) which is inhaled.

Blastomycosis (also known as “North American blastomycosis,” “Blastomycetic dermatitis,” and “Gilchrist’s disease”) is a fungal infection caused by the organism Blastomyces dermatitidis. Endemic to portions of North America, blastomycosis causes clinical symptoms similar to histoplasmosis.

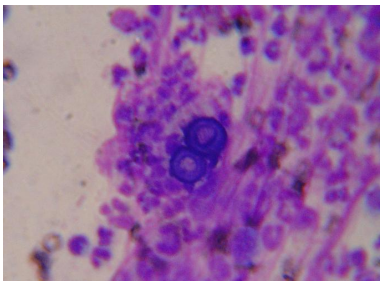

Figure: **Blastomycosis**: Blastomyces dermatitidis, the causative agent of blastomycosis.

Symptoms

Blastomycosis can present in one of the following ways:

- A flu-like illness with fever, chills, myalgia, headache, and a nonproductive cough which resolves within days
- An acute illness resembling bacterial pneumonia, with symptoms of high fever, chills, a productive cough, and pleuritic chest pain
- A chronic illness that mimics tuberculosis or lung cancer, with symptoms of low-grade fever, a productive cough, night sweats, and weight loss
- A fast, progressive, and severe disease that manifests as ARDS, with fever, shortness of breath, tachypnea, hypoxemia, and diffuse pulmonary infiltrates
- Skin lesions, usually asymptomatic, that appear as ulcerated lesions with small pustules at the margins
- Bone lytic lesions that can cause bone or joint pain.
- Prostatitis may be asymptomatic or may cause pain on urinating. Laryngeal involvement causes hoarseness.

Infection occurs by inhalation of the fungus from its natural soil habitat. Once inhaled in the lungs, Blastomycosis multiply and may disseminate through the blood and lymphatics to other organs, including the skin, bone, genitourinary tract, and brain. The incubation period is 30 to 100 days, although infection can be asymptomatic.

Diagnosis

Once suspected, the diagnosis of blastomycosis can usually be confirmed by demonstration of the characteristic, broad-based budding organisms in sputum or tissues by KOH prep, cytology, or histology. Tissue biopsy of skin or other organs may be required in order to diagnose extra-pulmonary disease. Blastomycosis is histologically associated with granulomatous nodules. Commercially available urine antigen testing appears to be quite sensitive in suggesting the diagnosis in cases where the organism is not readily detected. While culture of the organism remains the definitive diagnostic standard, its slow growing nature can lead to delays in treatment of up to several weeks.

Treatment

Itraconazole given orally is the treatment of choice for most forms of the disease. Ketoconazole may also be used. Cure rates are high, and the treatment over a period of months is usually well tolerated. Amphotericin B is considerably more toxic, and is usually reserved for immunocompromised patients who are critically ill and those with central nervous system disease. Fluconazole has also been tested on patients in Canada.

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15.14E: Other Fungi Involved in Respiratory Disease

Sporotrichosis is a disease caused by the fungus *Sporothrix schenckii*.

Learning Objectives

- Compare and contrast the various forms of sporotrichosis: cutaneous/skin, pulmonary and disseminated sporotrichosis

Key Points

- In cases of sporotrichosis affecting the lungs, the fungal spores enter through the respiratory pathways.
- Sporotrichosis progresses slowly – the first symptoms may appear from one to 12 weeks (average three weeks) after the initial exposure to the fungus.
- Forms and symptoms of sporotrichosis include: cutaneous or skin sporotrichosis; pulmonary sporotrichosis; and disseminated sporotrichosis.

Key Terms

- **fungus**: Any member of the kingdom Fungi; a eukaryotic organism typically having chitin cell walls but no chlorophyll or plastids. Fungi may be unicellular or multicellular.
- **Sporotrichosis**: A disease caused by the infection of the fungus Sporothrix schenckii, usually affecting the skin, although other rare forms can affect the lungs, joints, bones, and even the brain. Because roses can spread the disease, it is often referred to as rose-thorn or rose-gardeners' disease.

Sporotrichosis (also known as "Rose gardener's disease") is caused by the infection of the fungus *Sporothrix schenckii* . This fungal disease usually affects the skin, although other rare forms can affect the lungs, joints, bones, and even the brain. Because roses can spread the disease, it is one of a few diseases referred to as rose-thorn or rose-gardeners' disease.

Because S. schenckii is naturally found in soil, hay, sphagnum moss, and plants, it usually affects farmers, gardeners, and agricultural workers. It enters through small cuts and abrasions in the skin to cause the infection. In cases of sporotrichosis affecting the lungs, the fungal spores enter through the respiratory pathways. Sporotrichosis can also be acquired from handling cats with the disease; it is an occupational hazard for veterinarians.

Sporotrichosis progresses slowly – the first symptoms may appear from one to 12 weeks (average three weeks) after the initial exposure to the fungus. Serious complications can also develop in patients who have a compromised immune system.

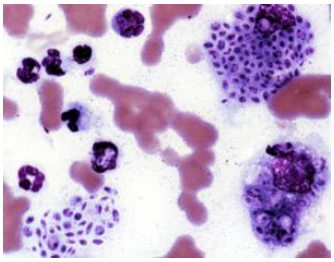

Figure: **Sporotrichosis**: Cytologic preparation from a case of feline sporotrichosis; phagocytic cells show numerous variably-shaped yeast forms within.

Forms and symptoms of sporotrichosis include: cutaneous or skin sporotrichosis; pulmonary sporotrichosis; and disseminated sporotrichosis.

Cutaneous or skin sporotrichosis: This is the most common form of the disease. Symptoms include nodular lesions or bumps in the skin at the point of entry and also along lymph nodes and vessels. The lesion starts off small and painless, and ranges in color from pink to purple. Left untreated, the lesion becomes larger and looks similar to a boil. More lesions will appear, until a chronic ulcer develops. Usually, cutaneous sporotrichosis lesions occur in the finger, hand, and arm.

Pulmonary sporotrichosis: This rare form of the disease occurs when S. schenckii spores are inhaled. Symptoms include productive coughing, nodules and cavitations of the lungs, fibrosis, and swollen hilar lymph nodes. Patients with this form of sporotrichosis are susceptible to developing tuberculosis and pneumonia.

Disseminated sporotrichosis: this occurs when the infection spreads from the primary site to secondary sites in the body and develops into a rare and critical form. The infection can spread to joints and bones (called osteoarticular sporotrichosis) as well as the central nervous system and the brain (called sporotrichosis meningitis). The symptoms include weight loss, anorexia, and the appearance of bony lesions.

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SECTION OVERVIEW

15.15: Microbial Diseases of the Digestive System

Topic hierarchy

15.15A: Anatomy of the Digestive System

15.15B: Normal Gastrointestinal Microbiota

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15.15A: Anatomy of the Digestive System

The human gastrointestinal tract refers to the stomach and intestine, and sometimes to all the structures from the mouth to the anus.

Learning Objectives

- Outline the anatomical organization of the digestive system

Key Points

- The major organs of the digestive system are the stomach and intestine.
- The upper gastrointestinal tract consists of the esophagus, stomach, and duodenum.
- The lower gastrointestinal tract includes the small intestine and the large intestine.
- Digestive juices are produced by the pancreas and the gallbladder.
- The small intestine includes the duodenum, jejunum, and ileum.
- The large intestine includes the cecum, colon, rectum, and anus.

Key Terms

- **upper gastrointestinal tract**: This tract consists of the esophagus, stomach, and duodenum.
- **lower gastrointestinal tract**: This tract includes most of the small intestine and all of the large intestine.

The human gastrointestinal tract refers to the stomach and intestine, and sometimes to all the structures from the mouth to the anus.

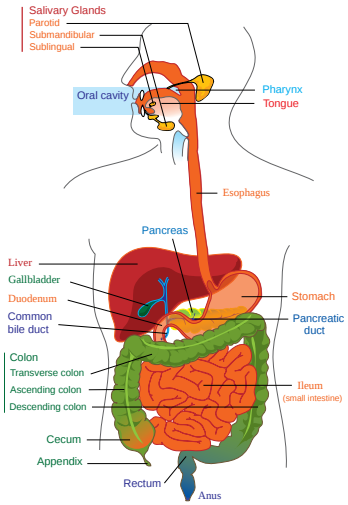

Figure: **Upper and lower gastrointestinal tract**: The major organs of the human gastrointestinal system.

Upper Gastrointestinal Tract

The upper gastrointestinal tract consists of the esophagus, stomach, and duodenum. The exact demarcation between upper and lower can vary. Upon gross dissection, the duodenum may appear to be a unified organ, but it is often divided into two parts based upon function, arterial supply, or embryology.

The upper gastrointestinal tract includes the:

- Esophagus, the fibromuscular tube that food passes through—aided by peristaltic contractions—the pharynx to the stomach.
- Stomach, which secretes protein -digesting enzymes called proteases and strong acids to aid in food digestion, before sending the partially digested food to the small intestines.
- Duodenum, the first section of the small intestine that may be the principal site for iron absorption.

Lower Gastrointestinal Tract

The lower gastrointestinal tract includes most of the small intestine and all of the large intestine. According to some sources, it also includes the anus.

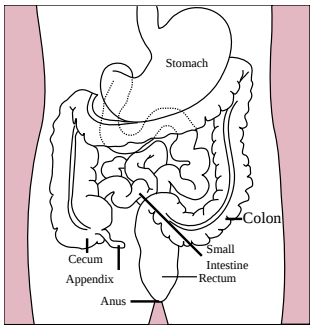

Figure: **Small intestine**: This image shows the position of the small intestine in the gastrointestinal tract.

The small intestine has three parts:

- Duodenum: Here the digestive juices from the pancreas (digestive enzymes) and the gallbladder (bile) mix together. The digestive enzymes break down proteins and bile and emulsify fats into micelles. The duodenum contains Brunner's glands that produce bicarbonate, and pancreatic juice that contains bicarbonate to neutralize hydrochloric acid in the stomach.
- Jejunum: This is the midsection of the intestine, connecting the duodenum to the ileum. It contains the plicae circulares and villi to increase the surface area of that part of the GI tract.
- Ileum: This has villi, where all soluble molecules are absorbed into the blood (through the capillaries and lacteals).

The large intestine has four parts:

1. Cecum, the vermiform appendix that is attached to the cecum.
2. Colon, which includes the ascending colon, transverse colon, descending colon, and sigmoid flexure. The main function of the colon is to absorb water, but it also contains bacteria that produce beneficial vitamins like vitamin K.
3. Rectum.
4. Anus.

The ligament of Treitz is sometimes used to divide the upper and lower GI tracts.

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15.15B: Normal Gastrointestinal Microbiota

Gut flora consist of microorganisms that live in the digestive tracts of animals and are the largest reservoir of human flora.

Learning Objectives

- Summarize the relationship between the nonpathogenic gastrointestinal microbiota and the human hosts

Key Points

- The relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather a mutualistic relationship.
- Gut flora perform functions, such as fermenting unused energy substrates, training the immune system, preventing growth of harmful bacteria, regulating the development of the gut, producing vitamins for the host, and producing hormones to direct the host to store fats.
- In certain conditions, some gutflora are thought to be capable of causing disease by producing infection or increasing cancer risk for the host.

Key Terms

- **commensal**: A term for a form of symbiosis in which one organism derives a benefit while the other is unaffected
- **microflora**: Microscopic plant life, especially the bacterial colonies found in the gut of normal, healthy animals and humans.

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora. In this context, gut is synonymous with intestinal, and flora with microbiota and microflora; the word microbiome is also in use.

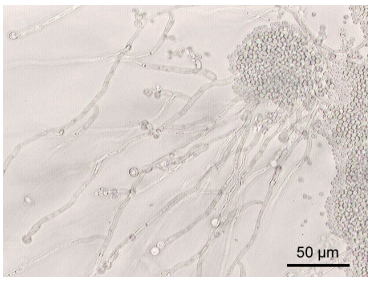

Figure: **Canidida albicans**: Candida albicans, a dimorphic fungus that grows as a yeast in the gut. Microscopic image (200-fold magnification) of Candida albicans ATCC 10231, grown on cornmeal agar medium with 1% Tween80.

The human body, consisting of about 10 trillion cells, carries about ten times as many microorganisms in the intestines. The metabolic activities performed by these bacteria resemble those of an organ, leading some to liken gut bacteria to a “forgotten” organ. It is estimated that these gut flora have around 100 times as many genes in aggregate as there are in the human genome.

Bacteria make up most of the flora in the colon and up to 60% of the dry mass of feces. Somewhere between 300 and 1000 different species live in the gut, with most estimates at about 500. However, it is probable that 99% of the bacteria come from about 30 or 40 species. Fungi and protozoa also make up a part of the gut flora, but little is known about their activities.

Research suggests that the relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather a mutualistic relationship. Though people can survive without gut flora, the microorganisms perform a host of useful functions, such as: fermenting unused energy substrates, training the immune system, preventing growth of harmful, pathogenic bacteria, regulating the development of the gut, producing vitamins for the host (such as biotin and vitamin K), and producing hormones to direct the host to store fats. However, in certain conditions, some species are thought to be capable of causing disease by producing infection or increasing cancer risk for the host.

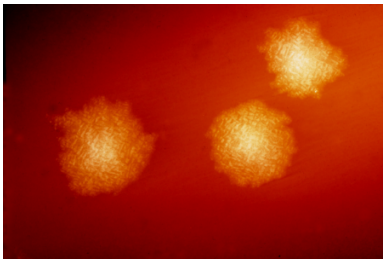

Figure: **This photograph depicts Clostridium difficile colonies after 48hrs growth on a blood agar plate; Magnified 4.8X.**: C. difficile, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAC). It accounts for approximately 15-25% of all episodes of AAC.

Over 99% of the bacteria in the gut are anaerobes, but in the cecum, aerobic bacteria reach high densities. Not all the species in the gut have been identified because most cannot be cultured, and identification is difficult. Populations of species vary widely among different individuals but stay fairly constant within an individual over time, even though some alterations may occur with changes in lifestyle, diet and age. An effort to better describe the microflora of the gut and other body locations has been initiated (such as the Human Microbiome Project). In 2009, scientists from INRA (France) highlighted the existence of a small number of species shared by all individuals constituting the human intestinal microbiota phylogenetic core. Most bacteria belong to the genera Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, and Bifidobacterium. Other genera, such as Escherichia and Lactobacillus, are present to a lesser extent. Species from the genus Bacteroides alone constitute about 30% of all bacteria in the gut, suggesting that this genus is especially important in the functioning of the host. The currently known genera of fungi of the gut flora include Candida, Saccharomyces, Aspergillus, and Penicillium. An enterotype is a classification of living organisms based on its bacteriological ecosystem in the human gut microbiome. Three human enterotypes have been discovered.

Bacteria in the gut fulfill a host of useful functions for humans, including digestion of unutilized energy substrates, stimulating cell growth, repressing the growth of harmful microorganisms, training the immune system to respond only to pathogens, and defending against some diseases.

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SECTION OVERVIEW

15.16: Bacterial Diseases of the Mouth

Topic hierarchy

15.16A: Tooth and Gum Infections

15.16B: Dental Caries

15.16C: Periodontal Disease

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15.16A: Tooth and Gum Infections

The mouth contains a wide variety of oral bacteria, but only a few specific species of bacteria are believed to cause tooth and gum infections.

Learning Objectives

- List the types of bacteria and issues associated with oral bacteria: Streptococci spp and Lactobaccilus acidophilus

Key Points

- Dental caries, also known as tooth decay or cavity, is a bacterial infection that causes demineralization and destruction of the hard tissues (enamel, dentin, and cementum).
- Tooth decay results from the production of acid by bacterial fermentation of the food debris accumulated on the tooth surface.
- Bacteria occupy the ecological niche provided by both the tooth surface and gingival epithelium. However, a highly efficient innate host defense system constantly monitors the bacterial colonization and prevents bacterial invasion of local tissues.
- Porphyromonas gingivalis is a Gram-negative oral anaerobe strongly associated with chronic adult periodontitis.
- Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products.

Key Terms

- **cavity**: A soft area in a decayed tooth.
- **plaque**: a clearing in a bacterial lawn caused by a virus
- **dental plaque**: Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products.
- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.

Tooth and Gum Infections

Dental caries, also known as tooth decay or cavity, is a bacterial infection that causes demineralization and destruction of the hard tissues (enamel, dentin, and cementum). This usually happens from the production of acid by bacterial fermentation of the food debris accumulated on the tooth surface. If demineralization exceeds saliva and other remineralization factors, such as from calcium and fluoridated toothpastes, these hard tissues progressively break down, producing dental caries (cavities, holes in the teeth). The bacteria most responsible for dental cavities are the mutans streptococci, most prominently Streptococcus mutans and Streptococcus sobrinus, and lactobacilli. If left untreated, the disease can lead to pain, tooth loss, and infection. Today, caries remain one of the most common diseases throughout the world.

The mouth contains a wide variety of oral bacteria, but only a few specific species of bacteria are believed to cause dental caries: Streptococcus mutans and Lactobacilli among them. Lactobacillus acidophilus, Actinomyces viscosus, Nocardia spp., and Streptococcus mutans are most closely associated with caries, in particular root caries. Bacteria collect around the teeth and gums in a sticky, creamy-colored mass called plaque, which serves as a biofilm. Some sites collect plaque more commonly than others. Grooves on the occlusal surfaces of molar and premolar teeth provide microscopic retention sites for plaque bacteria, as do the approximal sites. Plaque may also collect above or below the gingiva where it is referred to as supra- or sub-gingival plaque respectively.

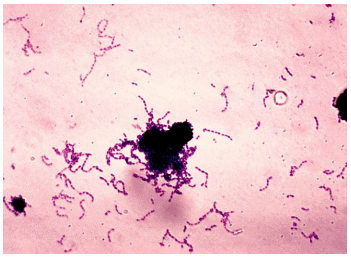

Figure: **Gram stain of Streptococcus mutans.**: Morphology is rod-like with chains when cultured on broth. Can cause subacute bacterial endocarditis and dental caries.

Oral bacteria have evolved mechanisms to sense their environment and evade or modify the host. Bacteria occupy the ecological niche provided by both the tooth surface and gingival epithelium. However, a highly efficient innate host defense system constantly monitors the bacterial colonization and prevents bacterial invasion of local tissues. A dynamic equilibrium exists between dental plaque bacteria and the innate host defense system. The oral cavity of the newborn baby does not contain bacteria but rapidly becomes colonized with bacteria such as Streptococcus salivarius. With the appearance of the teeth during the first year, colonization by Streptococcus mutans and Streptococcus sanguinis occurs as these organisms colonize the dental surface and gingiva. Other strains of streptococci adhere strongly to the gums and cheeks but not to the teeth. The gingival crevice area (supporting structures of the teeth) provides a habitat for a variety of anaerobic species. Bacteroides and spirochetes colonize the mouth around puberty.



Figure: **Dental caries**: This image shows destruction of a tooth by cervical decay from dental caries. This type of decay is also known as root decay.

The levels of oral spirochetes are elevated in patients with periodontal diseases. Among this group, Treponema denticola is the most studied and is considered one of the main etiological bacteria of periodontitis. Treponema denticola is a motile and highly proteolytic bacterium.

Spirochetes and fusi-form bacilli live as normal flora in the mouth, but the bacteria can cause infection and diseases to the oral cavity.

Porphyromonas gingivalis is a Gram-negative oral anaerobe strongly associated with chronic adult periodontitis. The bacterium produces a number of well-characterized virulence factors and can be manipulated genetically. The availability of the genome sequence is aiding our understanding of the biology of P. gingivalis and how it interacts with the environment, other bacteria, and the human host.

Aggregatibacter actinomycetemcomitans is considered an oral pathogen due to its virulence factors, its association with localized aggressive periodontitis in young adolescents, and studies indicating that it can cause bone loss.

Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products. Plaque is a biofilm on the surfaces of the teeth. This accumulation of microorganisms subject the teeth and gingival tissues to high concentrations of bacterial metabolites which results in dental disease. If not taken care of, via brushing or flossing, the plaque can turn into tartar (its hardened form) and lead to gingivitis or periodontal disease.

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15.16B: Dental Caries

Dental caries cause demineralization of the hard tissues and destruction of the organic matter of the tooth.

Learning Objectives

- Explain how dental caries can be prevented

Key Points

- Dentin is produced continuously throughout life by odontoblasts.
- Caries can be classified by location, etiology, rate of progression, and affected hard tissues.
- Enamel is a highly mineralized acellular tissue. Enamel rods, which are the basic unit of the enamel structure, run perpendicularly from the surface of the tooth to the dentin.
- There are four main criteria required for caries formation: a tooth surface (enamel or dentin), caries-causing bacteria, fermentable carbohydrates (such as sucrose), and time.
- Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone.
- The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus.
- The use of dental sealants is a means of prevention.
- Professional hygiene care consists of regular dental examinations and cleanings.
- An extraction can also serve as treatment for dental caries.
- In general, early treatment is less painful and less expensive than treatment of extensive decay.
- Recurrent caries, also described as secondary, are caries that appears at a location with a previous history of caries.
- Dentin is produced continuously throughout life by odontoblasts.
- Personal hygiene care consists of proper brushing and flossing daily. The purpose of oral hygiene is to minimize any etiologic agents of disease in the mouth.
- Primary diagnosis involves inspection of all visible tooth surfaces using a good light source, dental mirror and explorer. Dental radiographs (X-rays) may show dental caries before it is otherwise visible, in particular caries between the teeth.
- Caries can be classified by location, etiology, rate of progression, and affected hard tissues.
- In dentin from the deepest layer to the enamel, the distinct areas affected by caries are the advancing front, the zone of bacterial penetration, and the zone of destruction.
- Intrauterine and neonatal lead exposure promote tooth decay. Other divalent cations, such as cadmium, mimic the calcium ion and therefore exposure may promote tooth decay.
- From the deepest layer of the enamel to the enamel surface, the identified areas are the: translucent zone, dark zones, body of the lesion, and surface zone.
- Enamel is a highly mineralized acellular tissue. Enamel rods, which are the basic unit of the enamel structure, run perpendicularly from the surface of the tooth to the dentin.
- Some brands of smokeless tobacco contain high sugar content, increasing susceptibility to caries. Tobacco use is a significant risk factor for periodontal disease, which can cause the gingiva to recede.
- Reduced saliva is associated with increased caries.
- There are four main criteria required for caries formation: a tooth surface (enamel or dentin); caries-causing bacteria; fermentable carbohydrates (such as sucrose); and time.
- If demineralization exceeds saliva and other remineralization factors such as from calcium and fluoridated toothpastes, these tissues progressively break down, producing dental caries (cavities, holes in the teeth).
- The presentation of caries is highly variable.
- Bacteria collect around the teeth and gums in a sticky, creamy-coloured mass called plaque, which serves as a biofilm.
- Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone.
- The mineral content of teeth is sensitive to increases in acidity from the production of lactic acid.
- Radiographs are used for less visible areas of teeth and to judge the extent of destruction.
- Depending on the extent of tooth destruction, various treatments can be used to restore teeth to proper form, function, and aesthetics, but there is no known method to regenerate large amounts of tooth structure. Instead, dental health organizations advocate preventive and prophylactic measures, such as regular oral hygiene and dietary modifications, to avoid dental caries.

- Tooth decay disease is caused by specific types of bacteria that produce acid in the presence of fermentable carbohydrates such as sucrose, fructose, and glucose.
- Before the cavity forms, the process is reversible, but once a cavity forms, the lost tooth structure cannot be regenerated.
- The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus.

Key Terms

- **cementum**: A bony substance that covers the root of a tooth; cement.
- **enamel**: The hard covering on the exposed part of a tooth.
- **dentin**: The hard, dense calcareous material that makes up the bulk of a tooth

Dental caries, also known as tooth decay or a cavity, is an infection, usually bacterial in origin, that causes demineralization of the hard tissues (enamel, dentin, and cementum) and destruction of the organic matter of the tooth, usually by production of acid by hydrolysis of the food debris accumulated on the tooth surface. If demineralization exceeds saliva and other remineralization factors such as from calcium and fluoridated toothpastes, these tissues progressively break down, producing dental caries (cavities, holes in the teeth). The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus. If left untreated, the disease can lead to pain, tooth loss, and infection. Today, caries remain one of the most common diseases throughout the world.

Caries can be classified by location, etiology, rate of progression, and affected hard tissues. These forms of classification can be used to characterize a particular case of tooth decay in order to more accurately represent the condition to others and also indicate the severity of tooth destruction.

Tooth decay disease is caused by specific types of bacteria that produce acid in the presence of fermentable carbohydrates such as sucrose, fructose, and glucose. The mineral content of teeth is sensitive to increases in acidity from the production of lactic acid. To be specific, a tooth (which is primarily mineral in content) is in a constant state of back-and-forth demineralization and remineralization between the tooth and surrounding saliva. For people with little saliva, especially due to radiation therapies that may destroy the salivary glands, there also exists remineralization gel. These patients are particularly susceptible to dental caries. When the pH at the surface of the tooth drops below 5.5, demineralization proceeds faster than remineralization (meaning that there is a net loss of mineral structure on the tooth's surface). Most foods are in this acidic range and without remineralization result in the ensuing decay.

As the enamel and dentin are destroyed, the cavity becomes more noticeable. The affected areas of the tooth change color and become soft to the touch. Once the decay passes through enamel, the dentinal tubules, which have passages to the nerve of the tooth, become exposed, causing a toothache. The pain may worsen with exposure to heat, cold, or sweet foods and drinks. Dental caries can also cause bad breath and foul tastes. In highly progressed cases, infection can spread from the tooth to the surrounding soft tissues. Complications such as cavernous sinus thrombosis and Ludwig's angina can be life-threatening.

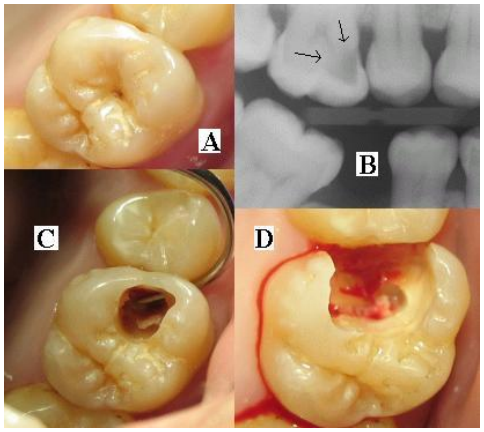

Figure: **Dental caries**: (A) A small spot of decay visible on the surface of a tooth. (B) The radiograph reveals an extensive region of demineralization within the dentin (arrows). (C) A hole is discovered on the side of the tooth at the beginning of decay removal. (D) All decay removed.

There are four main criteria required for caries formation: a tooth surface (enamel or dentin) caries-causing bacteria, fermentable carbohydrates (such as sucrose), and time. The caries process does not have an inevitable outcome, and different individuals will be susceptible to different degrees depending on the shape of their teeth, oral hygiene habits, and the buffering capacity of their saliva.

Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone. All caries occur from acid demineralization that exceeds saliva and fluoride remineralization, and almost all acid demineralization occurs where food (containing carbohydrate like sugar) is left on teeth. Though most trapped food is left between teeth, over 80% of cavities occur inside pits and fissures on chewing surfaces where brushing, fluoride, and saliva cannot reach to remineralize the tooth as they do on easy-to-reach surfaces that develop few cavities.

In most people, disorders or diseases affecting teeth are not the primary cause of dental caries. Ninety-six percent of tooth enamel is composed of minerals. These minerals, especially hydroxyapatite, will become soluble when exposed to acidic environments. Enamel begins to demineralize at a pH of 5.5. Dentin and cementum are more susceptible to caries than enamel because they have lower mineral content. Thus, when root surfaces of teeth are exposed from gingival recession or periodontal disease, caries can develop more readily. Even in a healthy oral environment, however, the tooth is susceptible to dental caries.

Bacteria in a person's mouth convert glucose, fructose, and most commonly sucrose (table sugar) into acids such as lactic acid through a glycolytic process called fermentation. If left in contact with the tooth, these acids may cause demineralization, which is the dissolution of its mineral content. The process is dynamic, however, as remineralization can also occur if the acid is neutralized by saliva or mouthwash.

At times, pit and fissure caries may be difficult to detect. Bacteria can penetrate the enamel to reach dentin, but then the outer surface may remineralize, especially if fluoride is present. These caries, sometimes referred to as "hidden caries", will still be visible on x-ray radiographs, but visual examination of the tooth would show the enamel intact or minimally perforated.

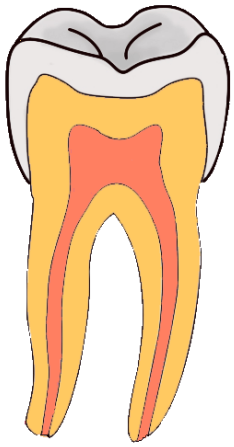

Figure: **Pit and fissure caries.**: The progression of pit and fissure caries resembles two triangles with their bases meeting along the junction of enamel and dentin.

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15.16C: Periodontal Disease

Plaque-induced inflammatory lesions make up the vast majority of periodontal diseases, which are divided into peridontitis or gingivitis.

Learning Objectives

- Differentiate between peridontitis and gingivitis

Key Points

- Peridontal tissues are the cementum, or the outer layer of the roots of teeth; the gingiva, or gums; the alveolar bone, or the bony sockets into which the teeth are anchored; and the periodontal ligament, which are the connective tissue fibers that run between the cementum and the alveolar bone.
- Periodontitis is an inflammatory disease affecting the periodontium, or the tissues that surround and support the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth.
- Periodontitis is caused by microorganisms that adhere to and grow on the tooth ‘s surfaces, along with an overly aggressive immune response against these microorganisms.
- In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. The gingival inflammation and bone destruction of peridontitis are largely painless.
- Gingivitis, or inflammation of the gums, is a non-destructive peridontal disease. The primary cause of gingivitis is poor oral hygiene which leads to the accumulation dental plaque at the gum line. Gingivitis can progress to periodontitis.
- Daily oral hygiene measures to prevent periodontal disease include brushing and flossing daily and using an antiseptic mouthwash.
- There are many surgical approaches used in treatment of advanced periodontitis, including open flap debridement, osseous surgery, as well as guided tissue regeneration and bone grafting.
- Several conditions and diseases, including Down syndrome, diabetes, and other diseases that affect one’s resistance to infection also increase susceptibility to periodontitis.
- The primary etiology (cause) of gingivitis is poor oral hygiene which leads to the accumulation of a mycotic and bacterial matrix at the gum line, called dental plaque. Other contributors are poor nutrition and underlying medical issues such as diabetes.
- Once successful periodontal treatment has been completed, with or without surgery, an ongoing regimen of “periodontal maintenance” is required.
- In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. Symptoms may include the following: redness or bleeding of gums, gum swelling that recurs, spitting out blood after brushing teeth, halitosis, or bad breath, and a persistent metallic taste in the mouth, gingival recession, resulting in apparent lengthening of teeth, deep pockets between the teeth and the gums, and loose teeth
- Periodontitis is caused by microorganisms that adhere to and grow on the tooth’s surfaces.
- The extent of disease refers to the proportion of the dentition affected by the disease in terms of percentage of sites. Generally, six probing sites around each tooth are recorded, as follows: mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, and distolingual.
- The severity of disease refers to the amount of periodontal ligament fibers that have been lost, termed clinical attachment loss.
- Smoking is a factor that increases the occurrence of periodontitis
- The 1999 classification system for periodontal diseases and conditions listed seven major categories of periodontal diseases, of which the last six are termed destructive periodontal disease because the damage is essentially irreversible. The seven categories are as follows:
- Gingivitis
- Chronic periodontitis
- Aggressive periodontitis
- Periodontitis as a manifestation of systemic disease
- Necrotizing ulcerative gingivitis/periodontitis
- Abscesses of the periodontium
- Combined periodontic-endodontic lesions

Key Terms

- **periodontitis**: An inflammatory disease that affects the periodontium—the tissues that surround and support the teeth–and can lead to tooth loss.
- **periodontium**: The specialized tissues that both surround and support the teeth, maintaining them in the maxillary and mandibular bones; the tissues including alveolar bone, cementum, gums, and periodontal ligament.
- **gingivitis**: Inflammation of the gums or gingivae.

Periodontal disease is a type of disease that affects one or more of the periodontal tissues, which include:

- the cementum, or the outer layer of the roots of teeth
- the gingiva, or gum tissue
- the alveolar bone, or the bony sockets into which the teeth are anchored
- the periodontal ligament, which are the connective tissue fibers that run between the cementum and the alveolar bone.

While many different diseases affect the tooth-supporting structures, plaque-induced inflammatory lesions make up the vast majority of periodontal diseases and have traditionally been divided into two categories: peridontitis or gingivitis.

Peridontitis

Periodontitis is an inflammatory disease affecting the periodontium, or the tissues that surround and support the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. Periodontitis is caused by microorganisms that adhere to and grow on the tooth's surfaces, along with an overly aggressive immune response against these microorganisms.

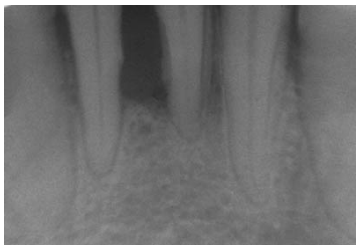

Figure: **Periodontal disease**: This radiograph shows significant bone loss between the two roots of a tooth (black region). The spongy bone has receded due to infection under the tooth, reducing the bony support for the tooth.

In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. Symptoms may include the following:

- Redness or bleeding of gums while brushing teeth, using dental floss, or biting into hard food
- Gum swelling that recurs
- Spitting out blood after brushing teeth
- Halitosis, or bad breath, and a persistent metallic taste in the mouth
- Gingival recession, resulting in apparent lengthening of teeth
- Deep pockets between the teeth and the gums, that are sites where the attachment has been gradually destroyed by collagen-destroying enzymes, known as collagenases
- Loose teeth, in the later stages

The gingival inflammation and bone destruction of peridontitis are largely painless. Hence, people may wrongly assume that painless bleeding after teeth cleaning is insignificant, although this may be a symptom of progressing periodontitis in that patient.

A diagnosis of periodontitis is established by inspecting the soft gum tissues around the teeth with a probe and by evaluating the patient's x-ray films to determine the amount of bone loss around the teeth.



Figure: **Gingivitis**: Severe gingivitis before (top) and after (bottom) treatment.

Gingivitis

Gingivitis, or inflammation of the gums, is a non-destructive peridontal disease. The primary cause of gingivitis is poor oral hygiene which leads to the accumulation of bacterial matrix at the gum line, called dental plaque. Other contributors are poor nutrition and underlying medical issues such as diabetes.

In some people, gingivitis progresses to periodontitis –- with the destruction of the gingival fibers, the gum tissues separate from the tooth, forming pockets between the tooth and gum. Subgingival microorganism (those that exist under the gum line) colonize the periodontal pockets and cause further inflammation in the gum tissues and progressive bone loss.

If left undisturbed, microbic plaque calcifies to form calculus, which is commonly called tartar. Calculus above and below the gum line must be removed completely by the dental hygienist or dentist to treat gingivitis and periodontitis. Although the primary cause of both gingivitis and periodontitis is the microbic plaque that adheres to the tooth surface, there are many other modifying factors. A very strong risk factor is one's genetic susceptibility. Several conditions and diseases, including Down syndrome, diabetes, and other diseases that affect one's resistance to infection also increase susceptibility to periodontitis.

Prevention

Daily oral hygiene measures to prevent periodontal disease include:

- Brushing teeth properly at least twice daily, with the patient attempting to direct the toothbrush bristles underneath the gum-line, to help disrupt the bacterial-mycotic growth and formation of subgingival plaque.
- Flossing daily and using interdental brushes as well as cleaning behind the last tooth, the third molar, in each quarter.
- Using an antiseptic mouthwash. Chlorhexidine gluconate-based mouthwash in combination with careful oral hygiene may cure gingivitis, although they cannot reverse any attachment loss due to periodontitis.
- Using periodontal trays to maintain dentist-prescribed medications at the source of the disease. The use of trays allows the medication to stay in place long enough to penetrate the biofilms where the microorganism are found.

Regular dental check-ups and professional teeth cleaning as required. Dental check-ups serve to monitor the person's oral hygiene methods and levels of attachment around teeth, identify any early signs of periodontitis, and monitor response to treatment.

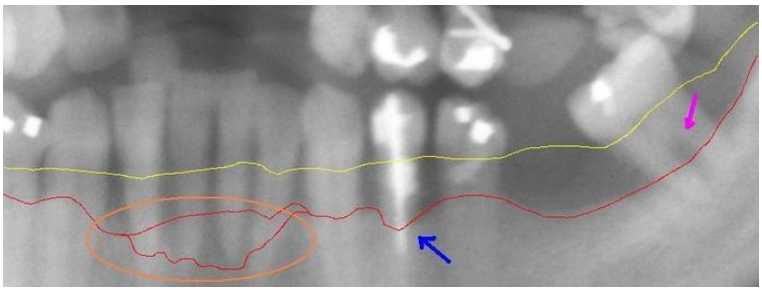

Figure: **Extensive periodontal disease**: This section from a panoramic x-ray film depicts the teeth of the lower left quadrant, exhibiting generalized severe bone loss of 30–80%. The red line depicts the existing bone level, and the yellow line depicts where the gingiva was originally (1–2 mm above the bone), prior to the patient developing periodontal disease. The pink arrow, on the right, points to a furcation involvement, or the loss of enough bone to reveal the location at which the individual roots of a molar begin to branch from the single root trunk; this is a sign of advanced periodontal disease.

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SECTION OVERVIEW

15.17: Bacterial Diseases of the Digestive System

Topic hierarchy

15.17A: Bacterial Gastroenteritis

15.17B: Staphylococcal Food Poisoning

15.17C: Salmonellosis

15.17D: Typhoid Fever

15.17E: Cholera

15.17F: Noncholera Vibrios

15.17G: Pathogenic Escherichia coli

15.17H: Campylobacter

15.17I: Peptic Ulcer Disease

15.17J: Listeriosis

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15.17A: Bacterial Gastroenteritis

Gastroenteritis is characterized by inflammation of the gastrointestinal tract that involves both the stomach and the small intestine.

Learning Objectives

- Describe the cause and effect of bacterial gastroenteritis

Key Points

- Gastroenteritis typically involves both diarrhea and vomiting, or less commonly, presents with only one or the other.
- Transmission rates are also related to poor hygiene, especially among children, in crowded households, and in those with pre-existing poor nutritional status.
- A supply of easily accessible uncontaminated water and good sanitation practices are important for reducing rates of infection and clinically significant gastroenteritis.

Key Terms

- **inflammation**: A condition of any part of the body, consisting in congestion of the blood vessels, with obstruction of the blood current, and growth of morbid tissue. It is manifested outwardly by redness and swelling, attended with heat and pain.
- **gastroenteritis**: Inflammation of the mucous membranes of the stomach and intestine; often caused by an infection.

Gastroenteritis is a medical condition characterized by inflammation ("-itis") of the gastrointestinal tract that involves both the stomach ("gastro"-) and the small intestine ("entero"-), resulting in some combination of diarrhea, vomiting, and abdominal pain and cramping. Although unrelated to influenza, it has also been called 'stomach flu' and 'gastric flu'.

Globally, most cases in children are caused by rotavirus. Less common causes include other bacteria (or their toxins) and parasites. Transmission may occur due to consumption of improperly prepared foods, contaminated water, or via close contact with individuals who are infectious. The foundation of management for this illness is adequate hydration. For mild or moderate cases, this can typically be achieved via oral rehydration solution. For more severe cases, intravenous fluids may be needed. Gastroenteritis primarily affects children and those in the developing world. Gastroenteritis typically involves both diarrhea and vomiting, or less commonly, presents with only one or the other. Abdominal cramping may also be present.

Signs and symptoms usually begin 12–72 hours after contracting the infectious agent. Some bacterial infections may be associated with severe abdominal pain and may persist for several weeks. In the developed world, *Campylobacter jejuni* is the primary cause of bacterial gastroenteritis, with half of these cases associated with exposure to poultry. In children, bacteria are the cause in about 15% of cases, with the most common types being *Escherichia coli*, *Salmonella*, *Shigella*, and *Campylobacter* species. If food becomes contaminated with bacteria and remains at room temperature for a period of several hours, the bacteria multiply and increase the risk of infection in those who consume the food. Toxigenic *Clostridium difficile* is an important cause of diarrhea that occurs more often in the elderly. Infants can carry these bacteria without developing symptoms. It is a common cause of diarrhea in those who are hospitalized and is frequently associated with antibiotic use. *Staphylococcus aureus* infectious diarrhea may also occur in those who have used antibiotics. "Traveler's diarrhea" is usually a type of bacterial gastroenteritis. Acid-suppressing medication appears to increase the risk of significant infection after exposure to a number of organisms, including *Clostridium difficile*, *Salmonella*, and *Campylobacter* species.

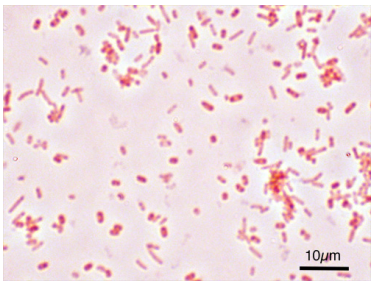

Figure: **Salmonella Typhimurium**: Salmonella enterica serovar Typhimurium as seen with a microscope at 1000 fold magnification and following Gram staining. Salmonella is a common cause of gastroenteritis in children.

Transmission rates are also related to poor hygiene, especially among children, in crowded households, and in those with pre-existing poor nutritional status. After developing tolerance, adults may carry certain organisms without exhibiting signs or

symptoms, and thus act as natural reservoirs of contagion. While some agents (such as *Shigella*) only occur in primates, others may occur in a wide variety of animals (such as *Giardia*).

Gastroenteritis is typically diagnosed clinically, based on a person's signs and symptoms. Determining the exact cause is usually not needed as it does not alter management of the condition. However, stool cultures should be performed in those with blood in the stool, those who might have been exposed to food poisoning, and those who have recently traveled to the developing world. Electrolytes and kidney function should also be checked when there is a concern about severe dehydration.

A supply of easily accessible uncontaminated water and good sanitation practices are important for reducing rates of infection and clinically significant gastroenteritis. Personal measures (such as hand washing) have been found to decrease incidence and prevalence rates of gastroenteritis in both the developing and developed world by as much as 30%.

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15.17B: Staphylococcal Food Poisoning

Staphylococcal toxins are a common cause of food poisoning, as they can be produced in improperly-stored food.

Learning Objectives

- Recognize the causes of staphylococcal food poisoning

Key Points

- Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.
- Foodborne illness usually arises from improper handling, preparation, or storage of food.
- Good hygiene practices before, during, and after food preparation can reduce the chances of contracting an illness.

Key Terms

- **toxin**: A toxic or poisonous substance produced by the biological processes of biological organisms.
- **norovirus**: The genus of a number of species of virus, family Caliciviridae, causing human gastroenteritis, of which Norwalk virus is the prototype.

Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins. Staphylococcal toxins are a common cause of food poisoning, as they can be produced in improperly-stored food. The main coagulase-positive staphylococcus is *Staphylococcus aureus*. These bacteria can survive on dry surfaces, increasing the chance of transmission.

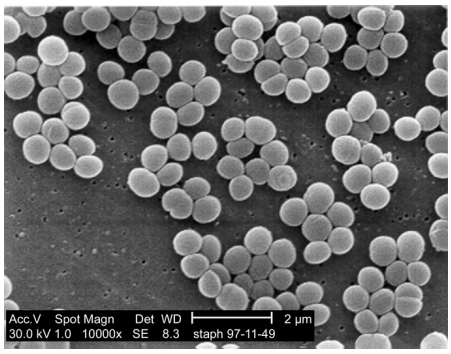

Figure: **Staphylococcus aureus**: Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.

Any *S. aureus* infection can cause the staphylococcal scalded skin syndrome, a cutaneous reaction to exotoxin absorbed into the bloodstream. It can also cause a type of septicaemia called pyaemia. The infection can be life-threatening. Problematically, Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major cause of hospital-acquired infections and is being recognized with increasing frequency in community-acquired infections.

Foodborne illness usually arises from improper handling, preparation, or food storage. Good hygiene practices before, during, and after food preparation can reduce the chances of contracting an illness. There is a consensus in the public health community that regular hand-washing is one of the most effective defenses against the spread of foodborne illness. The action of monitoring food to ensure that it will not cause foodborne illness is known as food safety.

Foodborne disease can also be caused by a large variety of toxins that affect the environment, such as pesticides or medicines in food, and naturally toxic substances such as poisonous mushrooms or reef fish. In the past, bacterial infections were thought to be more prevalent because few places had the capability to test for norovirus and no active surveillance was being done for this particular agent. Toxins for bacterial infections are delayed because the bacteria need time to multiply. Their symptoms are usually not seen until 12–72 hours or more after eating contaminated food.

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15.17C: Salmonellosis

Salmonellosis is an infection by the Salmonella bacteria that results in diarrhea, fever, vomiting, and abdominal cramps.

Learning Objectives

- Distinguish between nontyphoidal and typhoidal Salmonella

Key Points

- In severe cases, the Salmonella infection may spread from the intestines to the bloodstream, and then to other body sites, and can cause death unless the person is treated with antibiotics.
- The type of Salmonella usually associated with infections in humans, nontyphoidal Salmonella, is often contracted from contaminated food or reptiles.
- The Salmonella bacterium induces responses in the animal it is infecting, and this is what typically causes the symptoms, rather than any direct toxin that is produced.

Key Terms

- **typhoid fever**: An illness caused by the bacterium Salmonella typhi. Not to be confused with typhus.
- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.
- **arthritis**: Inflammation of a joint or joints causing pain and/or disability, swelling, and stiffness; and due to various causes such as infection, trauma, degenerative changes, or metabolic disorders.

Salmonellosis is an infection with the Salmonella bacteria. Most people infected with Salmonella develop diarrhea, fever, vomiting, and abdominal cramps 12 to 72 hours after infection. In most cases, the illness lasts four to seven days, and most people recover without treatment. However, in some cases the diarrhea may be so severe that the patient becomes dangerously dehydrated and must be taken to a hospital. At the hospital, the patient may receive intravenous fluids to treat the dehydration, and may be given medications to relieve symptoms, such as fever reducers. In severe cases, the Salmonella infection may spread from the intestines to the bloodstream, and then to other body sites, and can cause death unless the person is promptly treated with antibiotics. The elderly, infants, and those with impaired immune systems are more likely to develop severe illness. Some people afflicted with Salmonellosis later experience reactive arthritis, which can have long-lasting, disabling effects.

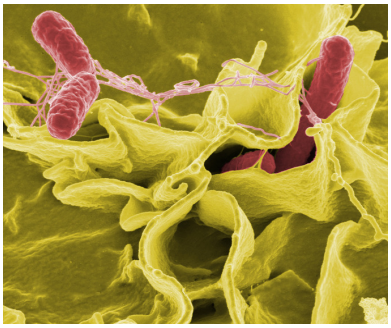

Figure: **Salmonella**: Salmonella is a genus of rod-shaped, gram-negative, non-spore-forming, predominantly motile enterobacteria (shown here in red).

Different Kinds of Salmonella

The different kinds of Salmonella include *S. bongori* and *S. enterica*. The type of Salmonella usually associated with infections in humans, nontyphoidal Salmonella, is usually contracted from: poultry, pork, and beef when the meat is prepared incorrectly or is infected with the bacteria after preparation; infected eggs, egg products, and milk when not prepared, handled, or refrigerated properly; reptiles (such as turtles, lizards, and snakes) which can carry the bacteria in their intestines; and tainted fruits and vegetables.

The typhoidal form of Salmonella can lead to typhoid fever. Typhoid fever is a life-threatening illness, and about four hundred cases are reported in the United States each year, with 75% of those acquired while traveling out of the country. It is carried only by humans and is usually contracted through direct contact with the fecal matter of an infected person. Typhoidal Salmonella is more

commonly found in poorer countries, where unsanitary conditions are more likely to occur, and can affect as many as 21.5 million people a year.

Salmonella Infection

The Salmonella bacterium induces responses in the animal it is infecting, and this is what typically causes the symptoms rather than any direct toxin that is produced. Symptoms are usually gastrointestinal, including nausea, vomiting, abdominal cramps, and bloody diarrhea with mucus. Headache, fatigue, and rose spots are also possible. These symptoms can be severe, especially in young children and the elderly. Symptoms last generally up to a week, and can appear 12 to 72 hours after ingesting the bacterium. After bacterial infections, reactive arthritis (Reiter's syndrome) can develop.

An infectious process can only begin after living salmonellae (not only their toxins) reach the gastrointestinal tract. Some of the microorganisms are killed in the stomach, while the surviving salmonellae enter the small intestine and multiply in tissues (this is the localized form). By the end of the incubation period, the macro-organisms are poisoned by endotoxins that are released from the dead salmonellae. The local response to the endotoxins is enteritis and gastrointestinal disorder. In the generalized form of the disease, salmonellae pass through the lymphatic system of the intestine into the blood of the patients (typhoid form) and are carried to various organs (liver, spleen, kidneys) to form secondary foci (septic form).

Endotoxins first act on affected organs' vascular and nervous systems, manifested by: increased permeability and decreased tone of the vessels, upset thermal regulation, vomiting, and diarrhea. In severe forms of the disease, enough liquid and electrolytes are lost to upset the body's metabolism of water and salt, decreasing the circulating blood volume and arterial pressure to enough of a degree to cause hypovolemic shock. Septic shock may also develop. Shock of mixed character (with signs of both hypovolemic and septic shock) is more common in severe salmonellosis. Oliguria and azotemia develop in severe cases as a result of kidney involvement due to hypoxia and bacteremia.

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15.17D: Typhoid Fever

Learning Objectives

- Summarize the four stages of untreated typhoid fever and methods of preventing it

Typhoid fever, also known as typhoid, is a common, worldwide bacterial disease. It is transmitted by the ingestion of food or water that has been contaminated with the feces of a person infected by the bacterium Salmonella typhi, serotype Typhi. The disease has been known by many names, such as gastric fever, abdominal typhus, infantile remittant fever, slow fever, nervous fever or pythogenic (originating from filth or putrefaction) fever. The name “typhoid” means “resembling typhus” and comes from the neuropsychiatric symptoms common to typhoid and typhus. The term “enteric fever” is a collective term that refers to typhoid and paratyphoid. The impact of this disease fell sharply with the improved sanitation techniques of the 20th century.

STAGES

Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.

First stage: the temperature rises slowly and fever fluctuations are seen with relative bradycardia (slow pulse), malaise, headache and cough. Nose bleeds (epistaxis) are seen in 25% of cases and abdominal pain can occur. There is leukopenia (a decrease in the number of circulating white blood cells), with eosinopenia and relative lymphocytosis. The classic Widal test is negative in the first week.

Second stage: the patient lies prostrate with high fever in plateau around 40 °C (104 °F) and bradycardia, classically with a dicrotic pulse wave. Delirium is frequent; patients may be calm, but sometimes agitated. This delirium gives typhoid its nickname of “nervous fever”. Rose spots appear on the lower chest and abdomen in around a third of patients. The Widal test is strongly positive with antiO and antiH antibodies. Blood cultures may be still positive at this stage. (The major symptom of typhoid is that the fever usually rises in the afternoon in the first and second stages.)

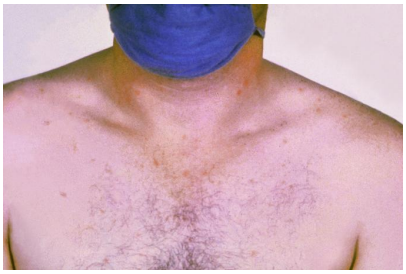

Figure: **Typhoid Fever**: Rose spots on the chest of a patient with typhoid fever due to the bacterium Salmonella typhi

Third stage: a number of complications can occur: intestinal hemorrhage due to bleeding in congested Peyer’s patches and intestinal perforation in the distal ileum.

Fourth stage: by the end of the third week the fever starts subsiding (defervescence). This carries on into the fourth and final week.

PREVENTION

The bacteria which cause typhoid fever may be spread through poor hygiene habits and public sanitation conditions and, sometimes, also by flying insects feeding on infected feces. Public education campaigns encouraging people to wash their hands after defecating and before handling food are an important component in controlling the spread of the disease. A person may become an asymptomatic carrier of typhoid fever, suffering no symptoms, but capable of infecting others.

DIAGNOSIS

Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagellar). In epidemics and less wealthy countries, after excluding malaria, dysentery or pneumonia, a therapeutic trial time with chloramphenicol is generally undertaken while awaiting the results of the Widal test, and cultures of the blood and stool. The Widal test is time-consuming and often, when a diagnosis is reached, it is too late to start an antibiotic regimen.

VACCINATION

There are two vaccines licensed for use for the prevention of typhoid: the live, oral Ty21a vaccine (sold as Vivotif Berna) and the injectable Typhoid polysaccharide vaccine (sold as Typhim Vi by Sanofi Pasteur and Typherix by GlaxoSmithKline).

TREATMENT

The rediscovery of oral rehydration therapy in the 1960s provided a simple way to prevent many of the deaths of diarrheal diseases in general. Where resistance is uncommon, the treatment of choice is a fluoroquinolone such as ciprofloxacin otherwise, a third-generation cephalosporin such as ceftriaxone or cefotaxime. Cefixime is a suitable oral alternative. Typhoid fever in most cases is not fatal. Antibiotics, such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, amoxicillin and ciprofloxacin have been commonly used to treat typhoid fever.

Key Points

- The impact of Typhoid fever fell sharply with the improved sanitation techniques of the 20th century.
- Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.
- Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagellar).

Key Terms

- **dicrotic**: A type of pulse associated with low systemic vascular resistance and a compliant aorta, e.g sepsis
- **Peyer's patch**: Peyer's patches (or aggregated lymphoid nodules) are usually found in the lowest portion of the small intestine, the ileum, in humans.
- **Widal test**: The agglutination test for typhoid fever.
- **eosinopenia**: Eosinopenia is a form of agranulocytosis where the number of eosinophil granulocyte is lower than expected; usually a predictor of bacterial infection.
- **lymphocytosis**: An increase in the number or proportion of lymphocytes in the blood.

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15.17E: Cholera

Cholera is an infection in the small intestine caused by the bacterium *Vibrio cholerae*.

Learning Objectives

- Describe the mode of transmission for Vibrio cholerae and the steps that can be taken to prevent this

Key Points

- The primary symptoms of cholera are profuse, painless diarrhea and vomiting of clear fluid.
- V. cholerae bacteria that survive the gastric juices produce the hollow cylindrical protein flagellin to make flagella, the cork-screw helical fibers they rotate to propel themselves through the mucus of the small intestine.
- A number of safe and effective oral vaccines for cholera are available.

Key Terms

- **flagella**: A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells.
- **electrolyte**: any of the various ions (such as sodium or chloride) that regulate the electric charge on cells and the flow of water across their membranes

Vibrio Cholerae

Cholera is an infection in the small intestine caused by the bacterium *Vibrio cholerae*. The primary symptoms of cholera are profuse, painless diarrhea and vomiting of clear fluid. These symptoms usually start suddenly, one to five days after ingestion of the bacteria. The diarrhea is frequently described as “rice water” in nature and may have a fishy odor. If the severe diarrhea is not treated with intravenous rehydration, it can result in life-threatening dehydration and electrolyte imbalances.



Figure: **Adult cholera patient**: A person with severe dehydration due to cholera – note the sunken eyes and decreased skin turgor which produces wrinkled hands.

Transmission

Cholera is typically transmitted by either contaminated food or water. In the developed world, seafood is the usual cause, while in the developing world it is more often water. Cholera is rarely spread directly from person to person. Both toxic and nontoxic strains exist.

Most *V. cholerae* bacteria, when consumed, do not survive the acidic conditions of the human stomach. The few surviving bacteria conserve their energy and stored nutrients during the passage through the stomach by shutting down much protein production. When the surviving bacteria exit the stomach and reach the small intestine, they need to propel themselves through the thick mucus that lines the small intestine to get to the intestinal walls, where they can thrive. *V. cholerae* bacteria begin production of the hollow cylindrical protein flagellin to make flagella. These flagella are cork-screw helical fibers that rotate to propel the bacteria through the mucus of the small intestine.

Once the cholera bacteria reach the intestinal wall, they no longer need the flagella to move. The bacteria stop producing the protein flagellin, again conserving energy and nutrients by changing the mix of proteins they manufacture in response to the changed chemical surroundings. The *V. cholerae* start producing the toxic proteins that give the infected person a watery diarrhea.

The diarrhea carries new generations of *V. cholerae* bacteria out into the drinking water of the next host if proper sanitation measures are not in place. A rapid dip-stick test is available to determine the presence of *V. cholerae* in a water supply. Samples

that test positive should be further tested to determine antibiotic resistance. In epidemic situations, a clinical diagnosis may be made by taking a patient history and doing a brief examination. Treatment is usually started without or before confirmation by laboratory analysis. Although cholera may be life-threatening, prevention of the disease is normally straightforward if proper sanitation practices are followed. In developed countries, due to nearly universal advanced water treatment and sanitation practices, cholera is no longer a major health threat.

Breaking the Transmission Path

Effective sanitation practices, if instituted and adhered to in time, are usually sufficient to stop an epidemic. There are several points along the cholera transmission path at which its spread may be halted.

- Sterilization or proper disposal and treatment of infected fecal waste water produced by cholera victims and all contaminated materials (e.g. clothing, bedding, etc.) is essential. All materials that come in contact with cholera patients should be sanitized by washing in hot water, using chlorine bleach if possible. Hands that touch cholera patients or their clothing, bedding, etc., should be thoroughly cleaned and disinfected with chlorinated water or other effective antimicrobial agents.
- Antibacterial treatment of general sewage by chlorine, ozone, ultraviolet light or other effective treatment before it enters the waterways or underground water supplies helps prevent undiagnosed patients from inadvertently spreading the disease.
- Warnings about possible cholera contamination should be posted around contaminated water sources with directions on how to decontaminate the water (boiling, chlorination etc.) for possible use.
- All water used for drinking, washing, or cooking should be sterilized by either boiling, chlorination, ozone water treatment, ultraviolet light sterilization (e.g. by solar water disinfection), or antimicrobial filtration in any area where cholera may be present.
- Public health education and adherence to appropriate sanitation practices are of primary importance to help prevent and control transmission of cholera and other diseases.

Prevention and Treatment

A number of safe and effective oral vaccines for cholera are available. In most cases, cholera can be successfully treated with oral rehydration therapy (ORT), which is effective, safe, and simple to administer. Rice-based solutions are more efficient than glucose-based ones. In cases of severe dehydration, intravenous rehydration may be necessary. Antibiotic treatments for one to three days shorten the course of the disease and reduce the symptoms. People will recover without them, however, if sufficient hydration is maintained. Doxycycline is typically used first line, although some strains of V. cholerae have shown resistance. Testing for resistance during an outbreak can help determine appropriate future choices. Other antibiotics proven to be effective include cotrimoxazole, erythromycin, tetracycline, chloramphenicol, and furazolidone. Fluoroquinolones, such as norfloxacin, also may be used, but resistance has been reported.

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15.17F: Noncholera Vibrios

Vibrio is a Gram-negative bacteria possessing a curved rod shape (comma shape), several species of which can cause foodborne infection.

Learning Objectives

- Discuss the difference between cholera and noncholera causing Vibrios

Key Points

- Vibrio species are prevalent in estuarine and marine environments. Seven species can cause food borne infections associated with seafood.
- Patients with noncholera Vibrio wound infection or septicemia are much more ill and frequently have other medical conditions.
- Early medical intervention is paramount and consists of antimicrobial therapy, intensive medical therapy for disease symptoms, and surgical removal of infected tissues if necessary.

Key Terms

- **necrotizing fasciitis**: Necrotizing fasciitis, commonly known as flesh-eating disease or flesh-eating bacteria syndrome, is a rare infection of the deeper layers of skin and subcutaneous tissues, that easily spreads across the fascial plane within the subcutaneous tissue.
- **hemolysin**: any substance that damages the membranes of red blood cells and thus releases hemoglobin
- **septicemia**: A disease caused by the presence of pathogenic organisms, especially bacteria or their toxins in the bloodstream, characterized by chills and fever.
- **vibrio**: Any of several bacteria, of the genus Vibrio, shaped like a curved rod.

Vibrio is a genus of Gram-negative bacteria possessing a curved rod shape (comma shape). Several species of Vibro can cause food borne infection, usually associated with eating undercooked seafood. Vibrio species are prevalent in estuarine and marine environments. Seven species can cause food borne infections associated with seafood. Vibrio cholerae O1 and O139 serovtypes produce cholera toxin and are agents of cholera. Vibrio species are facultative anaerobes that test positive for oxidase and do not form spores. All members of the genus are motile and have polar flagella with sheaths.

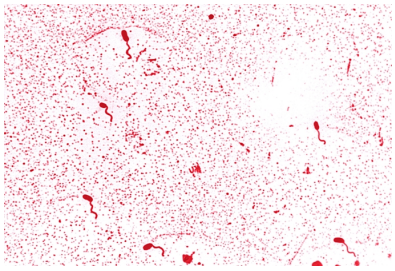

Figure: **Vibrio Cholerae**: Flagellar stain of V. cholerae

Patients with noncholera Vibrio wound infection or septicemia are much more ill and frequently have other medical conditions. Medical therapy consists of the following: prompt initiation of effective antibiotic therapy (doxycycline or a quinolone), intensive medical therapy with aggressive fluid replacement, vasopressors for hypotension and septic shock, early fasciotomy within 24 hours after development of clinical symptoms in patients with necrotizing fasciitis, early debridement of the infected wound, expeditious and serial surgical evaluation and intervention to prevent rapid deterioration, especially in patients with necrotizing fasciitis or compartment syndrome. Reconstructive surgery, such as skin graft, is indicated in the recovery phase.

Fecal-oral route infections in the terrestrial environment are responsible for epidemic cholera. Most strains cause gastroenteritis such as V. cholerae non-O1/O139 strains and Vibrio parahaemolytitcus strains capable of producing thermostable direct hemolysin (TDH) and/or TDH-related hemolysin. Vibrio vulnificus is responsible for seafood borne primary septicemia. Its infectivity depends primarily on the risk factors of the host. V. vulnificus infection has the highest fatality rate (50%) of any food borne pathogen. Four other species (V. mimicus, V. hollisae, V. fluvialis, and V. furnissii) can cause gastroenteritis. Some strains of these species produce known toxins, but the pathogenic mechanism is largely not understood.

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15.17G: Pathogenic Escherichia coli

Most E. coli strains are harmless, but some serotypes are pathogenic and can cause serious food poisoning in humans and other species.

Learning Objectives

- Distinguish between the different types of pathogenic E. coli in regards to classification and mode of transmission

Key Points

- Pathogenic E. coli strains can be categorized based on elements that can elicit an immune response in animals. The different categories are: O antigen, K antigen, H antigen, and F antigen in the lipopolysaccharide.
- In humans and in domestic animals, virulent strains of E. coli can cause gastroenteritis, urinary tract infections, and neonatal meningitis.
- Bacterial infections are usually treated with antibiotics.

Key Terms

- **bacteraemia**: The medical condition of having bacteria in the bloodstream.
- **lipopolysaccharide**: any of a large class of lipids conjugated with polysaccharides
- **flora**: the microorganisms that inhabit some part of the body, such as intestinal flora
- **enterohemorrhagic E. coli**: strains of the bacterium Escherichia coli that, when infecting humans, have been linked with the severe complication hemolytic-uremic syndrome

Escherichia coli (E. coli) is a Gram-negative, rod-shaped bacterium that is commonly found in the lower intestine of warm-blooded organisms (endotherms). Most E. coli strains are harmless, but some serotypes are pathogenic and can cause serious food poisoning in humans and other species. The harmless strains are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K2, and by preventing the establishment of pathogenic bacteria within the intestine.

Pathogenic E. coli

Pathogenic E. coli strains can be categorized based on elements that can elicit an immune response in animals, namely: O antigen, K antigen, H antigen, and F antigen in the lipopolysaccharide (LPS) molecules found in the outer membrane of the E. coli cell. The O antigen is a polymer of immunogenic repeating oligosaccharides which is used for serotyping E.coli. It should be noted though that antibodies towards several O antigens cross-react with other O antigens and partially to K antigens not only from E. coli, but also from other Escherichia species and Enterobacteriaceae species. There are two separate groups of K-antigen groups, named group I and group II (while a small in-between subset (K3, K10, and K54/K96) has been classified as group III). Group I consists of 100 kDa (large) capsular polysaccharides, while those in Group II, associated with extraintestinal diseases, are under 50 kDa in size.

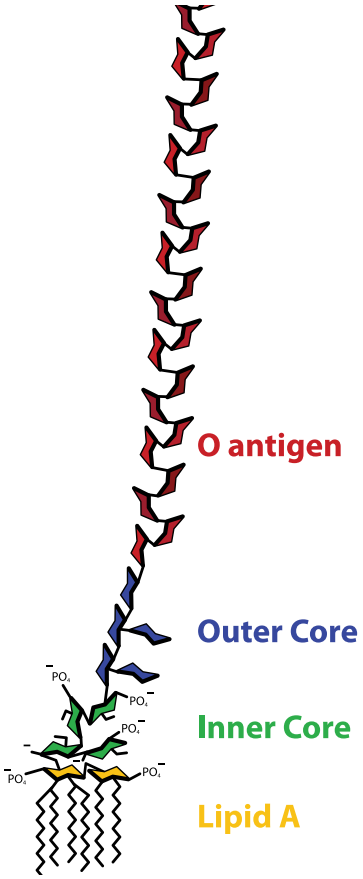

Figure: **Lipopolysaccharide**: Structure of a lipopolysaccharide showing the O antigen, core region and lipid A.

In humans and in domestic animals, virulent strains of E. coli can cause various diseases. In humans, gastroenteritis, urinary tract infections, and neonatal meningitis can occur. In rarer cases, virulent strains are also responsible for haemolytic-uremic syndrome, peritonitis, mastitis, septicemia, and Gram-negative pneumonia. Certain strains of E. coli produce potentially lethal toxins. Food poisoning caused by E. coli can result from eating unwashed vegetables or undercooked meat. If E. coli bacteria escape the intestinal tract through a perforation (for example from an ulcer, a ruptured appendix, or due to a surgical error) and enter the abdomen, they usually cause peritonitis that can be fatal without prompt treatment.

Transmission of pathogenic E. coli often occurs via fecal–oral transmission. Common routes of transmission include unhygienic food preparation, farm contamination due to manure fertilization, irrigation of crops with contaminated greywater or raw sewage, feral pigs on cropland, or direct consumption of sewage-contaminated water. According to the U.S. Food and Drug Administration, the fecal-oral cycle of transmission can be disrupted by cooking food properly, preventing cross-contamination, instituting barriers such as gloves for food workers, instituting health care policies so food industry employees seek treatment when they are ill, pasteurization of juice or dairy products and proper hand washing requirements.

Uropathogenic E. coli

Uropathogenic E. coli (UPEC) is responsible for approximately 90% of urinary tract infections (UTI) seen in individuals with ordinary anatomy. In ascending infections, fecal bacteria colonize the urethra and spread up the urinary tract to the bladder, as well as to the kidneys (causing pyelonephritis), or the prostate in males. Because women have a shorter urethra than men, they are 14 times more likely to suffer from an ascending UTI. Uropathogenic E. coli use P fimbriae (pyelonephritis-associated pili) to bind urinary tract endothelial cells and colonize the bladder. UPEC can evade the body's innate immune defences (e.g. the complement system) by invading superficial umbrella cells to form intracellular bacterial communities (IBCs). They also have the ability to form K antigen, capsular polysaccharides that contribute to biofilm formation. Descending infections in turn, though relatively rare, occur when E. coli cells enter the upper urinary tract organs (kidneys, bladder or ureters) from the blood stream.

E. coli and Meningitis

Neonatal meningitis is produced by a serotype of E. coli that contains a capsular antigen called K1. The colonization of the newborn's intestines with these stems, that are present in the mother's vagina, lead to bacteraemia, which leads to meningitis. Severe meningitis in the neonates are caused because of the absence of the IgM antibodies from the mother (these do not cross the placenta because FcRn only mediates the transfer of IgG), plus the fact that the body recognizes as self the K1 antigen, as it resembles the cerebral glicopeptides. In stool samples, microscopy will show Gram-negative rods, with no particular cell arrangement.

Treating E. coli

Bacterial infections are usually treated with antibiotics. However, the antibiotic sensitivities of different strains of E. coli vary widely. As Gram-negative organisms, E. coli are resistant to many antibiotics that are effective against Gram-positive organisms. Antibiotics which may be used to treat E. coli infection include amoxicillin, as well as other semisynthetic penicillins, many cephalosporins, carbapenems, aztreonam, trimethoprim-sulfamethoxazole, ciprofloxacin, nitrofurantoin, and the aminoglycosides. Researchers have actively been working to develop safe, effective vaccines to lower the worldwide incidence of E. coli infection.

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15.17H: Campylobacter

Campylobacter (meaning ‘twisted bacteria’) is a genus of bacteria that are Gram-negative, spiral, and microaerophilic.

Learning Objectives

- Discuss the method of transmission for Campylobacter

Key Points

- Campylobacter jejuni is now recognized as one of the main causes of bacterial foodborne disease in many developed countries.
- The common routes of transmission are fecal-oral, ingestion of contaminated food or water, and the eating of raw meat.
- It produces an inflammatory, sometimes bloody, diarrhea, periodontitis or dysentery syndrome, mostly including cramps, fever and pain.

Key Terms

- **microaerophilic**: living and thriving in an environment low in oxygen
- **enteritis**: Inflammation of the intestines, generally the small intestine, that may lead to diarrhea.
- **flagella**: A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells.

Description of Campylobacter Bacteria

Campylobacter is a genus of bacteria that are Gram-negative, spiral, and microaerophilic. The name means “twisted bacteria” because of the spiral formation; motile, with either unipolar or bipolar flagella, the organisms have a characteristic spiral/corkscrew appearance and are oxidase-positive.



Figure: **Epsilonproteobacteria**: Campylobacter bacteria are the number-one cause of food-related gastrointestinal illness in the United States. To learn more about this pathogen, ARS scientists are sequencing multiple Campylobacter genomes. This scanning electron microscope image shows the characteristic spiral, or corkscrew, shape of C. jejuni cells and related structures.

Campylobacter jejuni is now recognized as one of the main causes of bacterial foodborne disease in many developed countries. At least a dozen species of Campylobacter have been implicated in human disease, with C. jejuni and C. coli the most common. C. fetus is a cause of spontaneous abortions in cattle and sheep, as well as an opportunistic pathogen in humans.

Campylobacter species contain two flagellin genes in tandem for motility: flaA and flaB. These genes undergo intergenic recombination, further contributing to their virulence. Nonmotile mutants do not colonize.

Methods of Transmission and Treatment

The common routes of transmission are fecal-oral; the bacteria are introducted through ingestion of contaminated food or water and by the eating of raw meat. Infection produces an inflammatory, sometimes bloody diarrhea, periodontitis, or dysentery syndrome, mostly including cramps, fever and pain. The infection is usually self-limiting. In most cases symptomatic treatment by liquid and electrolyte replacement is enough in human infections. The use of antibiotics, on the other hand, is controversial.

Diagnosis

Symptoms typically last for five to seven days. The sites of tissue injury include the jejunum, the ileum, and the colon. Most strains of C. jejuni produce a toxin (cytolethal distending toxin) that hinders the cells from dividing and activating the immune system. This symptom helps the bacteria evade the immune system and survive for a limited time in the cells. A cholera-like enterotoxin was also once thought to be made, but this appears not to be the case. The organism produces diffuse, bloody, edematous, and exudative enteritis. Although rarely has the infection been considered a cause of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, no unequivocal case reports exist. In some cases, a Campylobacter infection can be the underlying cause of Guillain-Barré syndrome. Gastrointestinal perforation is a rare complication of ileal infection.

Diagnosis of the illness is made by testing a specimen of faeces (bowel motion). Standard treatment is now azithromycin and, on occassion, terbinafine. Quinolone antibiotics such as ciprofloxacin or levofloxacin are no longer as effective due to resistance. Dehydrated children may require intravenous (by vein) fluid treatment in a hospital. The illness is contagious, and children must be kept at home until they have been clear of symptoms for at least two days. Good hygiene is important to avoid contracting the illness or spreading it to others.

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15.17I: Peptic Ulcer Disease

A peptic ulcer, also known as peptic ulcer disease, is an erosion in the wall of the stomach, duodenum, or esophagus.

Learning Objectives

- List the causes of and treatments for peptic ulcer disease

Key Points

- 70–90% of peptic ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach.
- Diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer.
- Treatment of H. pylori usually leads to clearing of infection, relief of symptoms, and eventual healing of ulcers.
- Gas in the peritoneal cavity, shown on an erect chest x-ray or supine lateral abdominal x-ray, is an omen of perforated peptic ulcer disease, which requires emergency surgery.
- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.
- During the active phase, the base of the ulcer shows 4 zones: inflammatory exudate, fibrinoid necrosis, granulation tissue and fibrous tissue.
- A gastric peptic ulcer is a mucosal defect which penetrates the muscularis mucosae and muscularis propria, produced by acid-pepsin aggression.
- Ulcers are not purely an infectious disease and that psychological factors do play a significant role.
- Diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer.
- Gastric ulcers are most often localized on the lesser curvature of the stomach.
- Gas in the peritoneal cavity, shown on an erect chest X-ray or supine lateral abdominal X-ray, is an omen of perforated peptic ulcer disease.
- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours commonly accompanies ulcers.
- Typical ulcers tend to heal and recur and as a result the pain may occur for few days and weeks and then wane or disappear.

Key Terms

- **prostaglandin**: Any of a group of naturally occurring lipids derived from the C20 acid prostanoic acid; they have a number of physiological functions and may be considered to be hormones.
- **NSAID**: Any drug of the non-steroidal anti-inflammatory class used as a pain reliever.
- **gastrin**: A hormone that stimulates the production of gastric acid in the stomach.
- **gastritis**: Inflammation of the lining of the stomach, characterized by nausea, loss of appetite, and upper abdominal discomfort or pain.

A peptic ulcer, also known as peptic ulcer disease, is an erosion in the wall of the stomach, duodenum, or esophagus. As many as 70–90% of such ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.

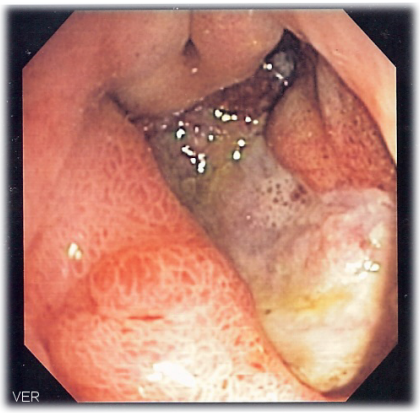

Figure: **Deep gastric ulcer**: This image, acquired via endoscope, shows a deep gastric ulcer.

Symptoms

Symptoms of a peptic ulcer include abdominal pain, classically near the stomach with severity relating to mealtimes, about three hours after eating a meal; bloating and abdominal fullness; nausea; copious vomiting; loss of appetite and weight loss; vomiting of blood; and melena, which are tarry, foul-smelling feces due to oxidized iron from hemoglobin. Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis. This is extremely serious and requires immediate surgery.

Causes

A major causative factor of ulcers is chronic inflammation due to Helicobacter pylori that colonizes the mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis, resulting in a defect in the regulation of gastrin production by that part of the stomach. Gastrin secretion can either be increased, or as in most cases, decreased, resulting in a too basic or too acidic stomach environment, respectively. A decrease in acid can promote H. pylori growth and an increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation.

Another major cause is the use of NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (cox-1), which is essential for the production of these prostaglandins.

Researchers also continue to look at stress as a possible cause, or at least complication, in the development of ulcers. There is debate as to whether psychological stress can influence the development of peptic ulcers. Burns and head trauma, however, can lead to physiologic stress ulcers, which are reported in many patients who are on mechanical ventilation.

Diagnosis

The diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer. In some cases, doctors may treat ulcers without diagnosing them with specific tests and observe whether the symptoms resolve, this indicating that their primary diagnosis was accurate.

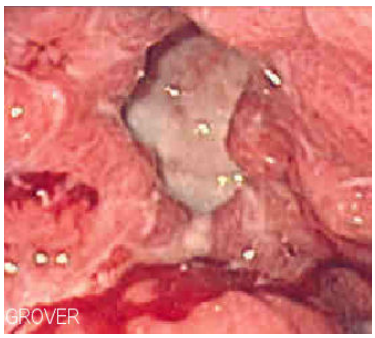

Figure: **Gastric ulcer**: This endoscopic image shows a gastric ulcer, which upon biopsy was shown to be gastric cancer.

Confirmation of the diagnosis is made with the help of tests such as endoscopies or barium contrast x-rays. The tests are typically ordered if the symptoms do not resolve after a few weeks of treatment. Tests are also given when first appear in a person who is

over age 45 or who has other symptoms such as weight loss, because stomach cancer can cause similar symptoms. Also, when severe ulcers resist treatment, particularly if a person has several ulcers or the ulcers are in unusual places, a doctor may suspect an underlying condition that causes the stomach to overproduce acid.

An esophagogastroduodenoscopy (EGD), a form of endoscopy, also known as a gastroscopy, is carried out on patients in whom a peptic ulcer is suspected. By direct visual identification, the location and severity of an ulcer can be described. Moreover, if no ulcer is present, EGD can often provide an alternative diagnosis.

If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract (which always contains some air) to the peritoneal cavity (which normally never contains air). This leads to “free gas” within the peritoneal cavity. If the patient stands erect, as when having a chest x-ray, the gas will float to a position underneath the diaphragm. Therefore, gas in the peritoneal cavity, shown on an erect chest x-ray or supine lateral abdominal x-ray, is an omen of perforated peptic ulcer disease.

Treatment



Figure: **Benign gastric ulcer**: This gastric ulcer was found in tissue removed during a gastrectomy.

Younger patients with ulcer-like symptoms are often treated with antacids. The ability of antacids to neutralize acidity by increasing the pH or blocking the secretion of acid by gastric cells is critical in reducing acidity in the stomach. Patients who are taking NSAIDs may also be prescribed a prostaglandin analogue in order to help prevent peptic ulcers by replacing the prostaglandins whose formation is blocked by NSAID use.

When H. pylori infection is present, the most effective treatments are combinations of two antibiotics, such as Clarithromycin, Amoxicillin, Tetracycline, and Metronidazole; and one proton pump inhibitor, sometimes in combination with antacids. In complicated, treatment-resistant cases, three antibiotics may be used together with a proton pump inhibitor. Treatment of H. pylori usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers. Recurrence of infection can occur and retreatment may be required, if necessary with other antibiotics.

Perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.

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15.17J: Listeriosis

Listeriosis is a bacterial infection caused by a Gram-positive, motile bacterium called Listeria monocytogenes.

Learning Objectives

- Discuss the mechanism of action for listeriosis

Key Points

- Listeriosis has a low incidence in humans and occurs in pregnant women, newborn infants, elderly patients, and patients who are immunocompromised.
- Listeria can invade through unusually tough barriers in humans: the blood-brain barrier and the feto-placental barrier, which contain high levels of cadherin protein on their membrane.
- The main route of acquisition of Listeria is through the ingestion of contaminated food products.

Key Terms

- **incidence**: a measure of the risk that a person develops a new condition within a specified period of time, usually a year
- **listeriosis**: An infectious disease of humans and animals caused by the bacteria Listeria monocytogenes and Listeria ivanovii, often through contaminated food.
- **meningitis**: Inflammation of the meninges, characterized by headache, neck stiffness and photophobia and also fever, chills, vomiting, and myalgia.
- **cadherin**: Any of a class of transmembrane proteins important in maintaining tissue structure.
- **blood-brain barrier**: a structure in the central nervous system (CNS) that keeps various substances found in the bloodstream out of the brain while allowing in the substances essential to metabolic function

Listeriosis is a bacterial infection caused by a Gram-positive, motile bacterium, *Listeria monocytogenes*. Listeriosis has a low incidence in humans and occurs in pregnant women, newborn infants, elderly patients, and patients who are immunocompromised. Pregnant women are the most susceptible and infection can lead to early delivery, infection of the newborn, and death of the baby.

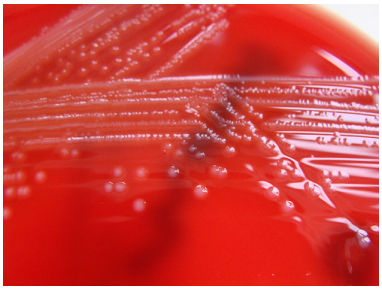

Figure: **Listeria monocytogenes**: A bacterial infection caused by a Gram-positive, motile bacterium, Listeria monocytogenes which is shown here on a blood agar plate.

The symptoms of listeriosis usually last 7–10 days, with the most common symptoms being fever, muscle aches, and vomiting. Diarrhea is another symptom, but less common. If the infection spreads to the nervous system it can cause meningitis, an infection of the covering of the brain and spinal cord.

Listeria originally evolved to invade membranes of the intestines, as an intracellular infection, and developed a chemical mechanism to do so. This involves a bacterial protein “internalin” which attaches to a protein on the intestinal cell membrane “cadherin. ” These adhesion molecules are also to be found in two other unusually tough barriers in humans – the blood-brain barrier and the feto-placental barrier, and this may explain the apparent affinity that Listeria has for causing meningitis and affecting babies in-utero. Particular strains of a food-borne bacteria are able to invade the heart, leading to serious and difficult-to-treat heart infections.

Listeria monocytogenes is ubiquitous in the environment. The main route of acquisition is by the ingestion of contaminated food products. Listeria has been isolated from raw meat, dairy products, vegetables, fruit and seafood. Soft cheeses, unpasteurized milk and unpasteurised pâté are potential dangers too. The main prevention is through the promotion of safe handling, cooking and consumption of food. This includes washing raw vegetables and cooking raw food thoroughly, as well as reheating leftover or

ready-to-eat foods, like hot dogs, until steaming hot. Another preventative measure is to advise high-risk groups such as pregnant women and immunocompromised patients to avoid unpasteurized pâtés and foods such as soft cheeses.

In the advent of listeriosis, bacteremia should be treated for two weeks, meningitis for three weeks, and brain abscess for at least six weeks. Ampicillin generally is considered the antibiotic of choice and gentamicin is added frequently for its synergistic effects. About 10 percent of serious listeria infections involve cardiac infections that are difficult to treat, with more than one-third proving fatal.

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SECTION OVERVIEW

15.18: Viral Diseases of the Digestive System

Topic hierarchy

15.18A: Mumps

15.18B: Hepatitis

15.18C: Viral Gastroenteritis

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15.18A: Mumps

Mumps was a common childhood viral disease, but widespread vaccination has now made it rare in developed countries.

Learning Objectives

- Analyze the cause, symptoms, and prevention of mumps

Key Points

- Mumps is a contagious disease that is spread from person to person through contact with respiratory secretions, such as saliva from an infected person. The common symptoms of mumps include inflammation of the salivary glands, pancreas, and testicles; fever; and headache.
- A physical examination confirms the presence of the swollen glands. Usually, the disease is diagnosed on clinical grounds and no confirmatory laboratory testing is needed.
- The most common preventative measure against mumps is a vaccination with a mumps vaccine. The vaccine may be given separately or as part of the routine MMR immunization vaccine which also protects against measles and rubella.
- Like many other viral illnesses, there is no specific treatment for mumps, other than supportive treatment. Death from mumps is very unusual. The disease is self-limiting, and general outcome is good. Known rare complications of mumps include infertility in men and profound hearing loss.

Key Terms

- **orchitis**: A painful inflammation of one or both testes.
- **salivary gland**: Any of several exocrine glands that produce saliva to break down carbohydrates in food enzymatically.
- **prodromal symptoms**: A prodrome is an early symptom (or set of symptoms) that might indicate the start of a disease before specific symptoms occur.
- **parotid gland**: Either of a pair of salivary glands located in front of, and below each ear in humans.

Mumps, also known as epidemic parotitis, was a common childhood viral disease caused by the mumps virus. Before the development of vaccination and the introduction of a vaccine in 1949, it was common worldwide, but now, outbreaks are largely confined to developed countries.

Symptoms

The common symptoms of mumps include inflammation of the salivary glands, pancreas, and testicles; fever, and headache. Swelling of the salivary glands, specifically the parotid gland, is known as parotitis, and it occurs in 60–70% of infections and 95% of patients with symptoms. Parotitis causes swelling and local pain, particularly when chewing. It can occur on one side but is more common on both sides in about 90% of cases. Painful inflammation of the testicles in mumps in known as orchitis. Other symptoms of mumps can include dry mouth, sore face and/or ears and occasionally, in more serious cases, loss of voice. In addition, up to 20% of persons infected with the mumps virus do not show symptoms, so it is possible to be infected and spread the virus without knowing it. Fever and headache are prodromal symptoms of mumps, together with malaise and loss of appetite.



Figure: **Child with mumps**: This child with mumps displays the typical swelling of the salivary glands caused by the mumps virus.

Causes

Mumps is a contagious disease that is spread from person to person through contact with respiratory secretions, such as saliva from an infected person. When an infected person coughs or sneezes, the droplets aerosolize and can enter the eyes, nose, or mouth of

another person. Mumps can also be spread by sharing food and drinks. The virus can survive on surfaces and then be spread after contact in a similar manner. A person infected with mumps is contagious from approximately six days before the onset of symptoms until about nine days after symptoms start. The incubation period can be anywhere from 14–25 days, but is more typically 16–18 days.

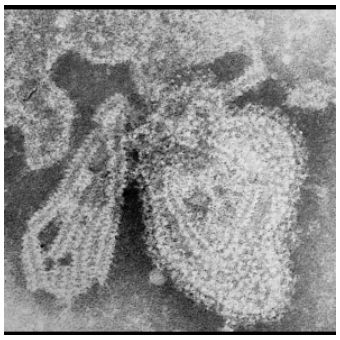

Figure: **Mumps virus**: This transmission electron micrograph (TEM) shows the ultrastructure of the mumps virus. It is a roughly spherical particle made up of layers of fatty lipids, large protein molecules, and nucleic acids. The virus is dotted with large protein "spikes" that enable it to gain entry to host cells. Inside lies a core of a single, long molecule of RNA wrapped up in protein that is released into the host cell.

Diagnostics

A physical examination confirms the presence of the swollen glands. Usually, the disease is diagnosed on clinical grounds, and no confirmatory laboratory testing is needed. If there is uncertainty about the diagnosis, a test of saliva or blood may be carried out. An estimated 20–30% of cases are asymptomatic. As with any inflammation of the salivary glands, the level of amylase in the blood is often elevated.

Prevention

The most common preventative measure against mumps is a vaccination with a mumps vaccine. The vaccine may be given separately or as part of the routine MMR immunization vaccine which also protects against measles and rubella. The MMR vaccine is given at ages 12–15 months and then again at four to six years.

Treatment and Complications

Like many other viral illnesses, there is no specific treatment for mumps. Symptoms may be relieved by the application of intermittent ice or heat to the affected neck/testicular area and by the acetaminophen or ibuprofen for pain relief. Warm salt water gargles, soft foods, and extra fluids may also help relieve symptoms. Patients are advised to avoid acidic foods and beverages, since these stimulate the salivary glands, which can be painful.

Death from mumps is very unusual. The disease is self-limiting, and general outcome is good, even if other organs are involved. Known complications of mumps include:

- In teenage males and men, complications from orchitis such as infertility or sub-fertility are rare, but present.
- Spontaneous abortion in about 27% of cases during the first trimester of pregnancy.
- Mild forms of meningitis in up to 10% of cases.
- Profound hearing loss is very rare, but mumps was the leading cause of acquired deafness before the advent of the mumps vaccine.

After the illness, life-long immunity to mumps generally occurs; re-infection is possible but tends to be mild and atypical.

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15.18B: Hepatitis

Hepatitis is the inflammation of the liver. Causes include viruses, bacterial infections, alcohol, autoimmune disorders, drugs, and toxins.

Learning Objectives

- Differentiate between acute and chronic hepatitis

Key Points

- Hepatitis is acute when it lasts less than six months and chronic when it persists longer.
- The initial symptoms of hepatitis are nonspecific flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhea, and headache.
- A diagnosis of hepatitis is usually made by a combination of blood work and physical examination. When the liver is inflamed, levels of certain liver enzymes that are found in the blood will be elevated. If a patient has viral hepatitis, the presence of the virus can be detected in the blood.
- There are many causes of liver inflammation or hepatitis. The most common cause of acute hepatitis is infection with the Hepatitis B, C, or D viruses. Bacterial diseases can also cause liver inflammation, such as tuberculosis and tick-borne diseases.
- Non-infectious causes of hepatitis include alcohol, autoimmune conditions, drugs, circulatory insufficiency, metabolic diseases, pregnancy, and toxins.
- For those with alcohol-induced hepatitis, cessation of drinking is recommended, as alcoholic hepatitis is often the beginning of more serious drinking-related liver disorders.

Key Terms

- **ascites**: An accumulation of fluid in the peritoneal cavity, frequently symptomatic of liver disease.
- **jaundice**: A yellowish pigmentation of the skin, the whites of the eyes (sclera), and other mucous membranes caused by increased levels of bilirubin in the blood that build up in extracellular fluid, usually due to liver disease.
- **cirrhosis**: A chronic disease of the liver caused by damage from toxins (including alcohol), metabolic problems, hepatitis, or nutritional deprivation. It is characterized by an increase of fibrous tissue and the destruction of liver cells.
- **hepatitis**: inflammation of the liver, sometimes caused by a viral infection

Hepatitis is the inflammation of the liver. The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring) and cirrhosis.

Hepatitis may occur with limited or no symptoms, but often leads to jaundice, poor appetite, and malaise. Hepatitis is acute when it lasts less than six months and chronic when it persists longer. A group of viruses, known as the hepatitis viruses, cause most cases of hepatitis worldwide, but it can also be due to toxins, notably alcohol, certain medications, some industrial organic solvents, and plants.

Symptoms

The initial symptoms of hepatitis are nonspecific flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhea, and headache. More specific symptoms, which can be present in acute hepatitis from any cause, are profound loss of appetite, aversion to smoking among smokers, dark urine, yellowing of the eyes and skin and abdominal discomfort. Physical findings are usually minimal, apart from jaundice and liver swelling. Some patients exhibit enlarged lymph nodes or enlargement of the spleen.



Figure: **Jaundice**: Jaundice, seen here as yellowing of the eyes, is often a symptom of hepatitis.

Acute Hepatitis

Acute viral hepatitis is more likely to be asymptomatic in younger people. Symptomatic individuals may present after convalescent stage of 7 to 10 days, with the total illness lasting 2 to 6 weeks.

A small proportion of people with acute hepatitis progress to acute liver failure, in which the liver is unable to clear harmful substances from the circulation, leading to confusion and coma due liver insufficiency, and unable to produce blood proteins, leading to peripheral edema and bleeding. This may become life-threatening and, occasionally, requires a liver transplant.

Chronic Hepatitis

Chronic hepatitis often leads to nonspecific symptoms, such as malaise, tiredness and weakness, and often causes no symptoms at all. It is commonly identified on blood tests performed either for screening or to evaluate nonspecific symptoms. The occurrence of jaundice indicates advanced liver damage. On physical examination, there may be enlargement of the liver.

Extensive damage and scarring of liver, known as cirrhosis, leads to weight loss, easy bruising and bleeding tendencies, peripheral edema and accumulation of ascites, or fluid in the abdominal cavity. Eventually, cirrhosis may lead to various complications, including esophageal varices, which are enlarged veins in the wall of the esophagus that can cause life-threatening bleeding; hepatic encephalopathy, which causes confusion and coma; and kidney dysfunction.

Diagnoses

A diagnosis of hepatitis is usually made by a combination of blood work and physical examination. When the liver is inflamed, levels of certain liver enzymes that are found in the blood will be elevated. If a patient has viral hepatitis, the presence of the virus can be detected in the blood. Patients with progressing liver damage will often display jaundice, or yellowing of the whites of the eyes and skin, and their livers will be visibly enlarged.

Causes

There are many causes of liver inflammation, or, hepatitis. The most common cause of acute hepatitis is infection with the Hepatitis B, C, or D viruses. Bacterial diseases can also cause liver inflammation, such as tuberculosis and tick-borne diseases.

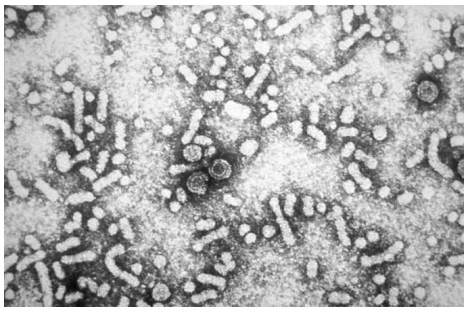

Figure: **Hepatitis B Virus**: The hepatitis B virus is a common cause of liver inflammtion.

Non-infectious causes of hepatitis include alcohol, autoimmune conditions, drugs, circulatory insufficiency, metabolic diseases, pregnancy, and toxins.

Alcohol is a significant cause of hepatitis worldwide. Usually alcoholic hepatitis comes after a period of increased alcohol consumption. Alcoholic hepatitis is characterized by a variable constellation of symptoms, which may include feeling unwell,

enlargement of the liver, development of fluid in the abdomen ascites, and a modest elevation of liver blood tests. Alcoholic hepatitis can vary from mild with only liver test elevation to severe liver inflammation with development of jaundice and liver failure.

Alcoholic hepatitis is distinct from cirrhosis caused by long-term alcohol consumption. Alcoholic hepatitis can occur in patients with chronic alcoholic liver disease and alcoholic cirrhosis. Alcoholic hepatitis by itself does not lead to cirrhosis, but cirrhosis is more common in patients with long-term alcohol consumption.

Treatment

Treatment of hepatitis typically involves treating the underlying condition that caused the inflammation.

In acute hepatitis caused by the hepatitis viruses, often, the liver inflammation will subside when the viral illness has subsided. Antiviral medications, such as interferon, can be used to treat the hepatitis viruses. There is currently a vaccination for Hepatitis B, but not for C or D. Similarly, hepatitis caused by a bacterial disease will typically resolve once the bacterial illness is treated with antibiotics.

For non-infectious causes of hepatitis, treatment of the underlying cause is necessary. For those with alcohol-induced hepatitis, cessation of drinking is recommended, as alcoholic hepatitis is often the beginning of more serious drinking-related liver disorders.

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15.18C: Viral Gastroenteritis

Gastroenteritis is caused by two different virus types in adults and children.

Learning Objectives

- Recognize the viruses that cause gastroenteritis and their mode of transmission

Key Points

- Rotaviruses typically causes gastroenteritis in children. These are double-stranded viruses, which have two coats or capsids.
- Noroviruses, which cause most adult cases of gastroenteritis, are fast mutating viruses.
- The key to the treatment of gastroenteritis is rehydration, either orally or, in severe cases, intravenously.

Key Terms

- **replication**: Process by which an object, person, place or idea may be copied mimicked or reproduced.
- **kbp**: kilobase pair
- **substitutions per site per year**: A DNA mutation where one DNA base pair is replaced with another; often used synonymous with the term mutation rate.

Gastroenteritis is a medical condition characterized by inflammation ("-itis") of the gastrointestinal tract that involves both the stomach ("gastro"-) and the small intestine ("entero"-), resulting in some combination of diarrhea, vomiting, abdominal pain and cramping. Gastroenteritis has also been referred to as gastro, stomach bug, and stomach virus. Although unrelated to influenza, it has also been called stomach flu and gastric flu.

Viruses that are known to cause gastroenteritis include rotavirus, norovirus, adenovirus, and astrovirus. Globally, Rotavirus is the most common cause of gastroenteritis in children, and produces similar incidence rates in both the developed and developing world. In adults, norovirus and Campylobacter are more common causes.

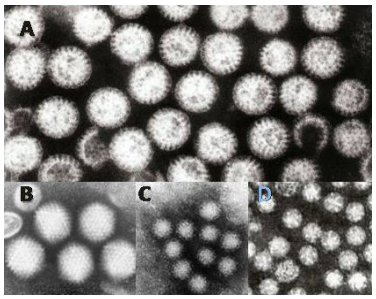

Figure: **Gastroenteritis Viruses**: Electron Micrographs of viruses that cause gastroenteritis in humans. A = rotavirus, B = adenovirus, C = norovirus and D = astrovirus. They are shown at the same magnification of approximately x 200,000

Viruses cause about 70% of episodes of infectious diarrhea in the pediatric age group. Rotavirus is a genus of double-stranded RNA virus in the family Reoviridae. Reoviruses are non-enveloped and have an icosahedral capsid composed of an outer and inner protein shell. The genomes of viruses in Reoviridae contains 10-12 segments which are grouped into three categories corresponding to their size: L (large), M (medium) and S (small). Segments range from ~ 3.9 kbp – 1kbp and each segment encodes 1-3 proteins. Since these viruses have dsRNA genomes, replication occurs exclusively in the cytoplasm and the virus encodes several proteins which are needed for replication.

The virus can enter the host cell via a receptor on the cell surface. The receptor is not known. After binding to the receptor the outer shell is partially digested to allow cell entry. The inner shell particle then enters the cytoplasm by a yet unknown process to start replication. Viral particles begin to assemble in the cytoplasm 6–7 hours after infection.

Rotavirus is a less common cause in adults due to their acquired immunity. Norovirus is the leading cause of gastroenteritis among adults in America, causing greater than 90% of outbreaks. Noroviruses contain an RNA genome of approximately 7.5 kbp, encoding a major structural protein (VP1) and a minor capsid protein (VP2). The virus particles demonstrate an amorphous surface structure when visualized using electron microscopy and are between 27-38 nm in size.

The most variable region between different viruses of the same type is a portion of the viral capsid. Specifically a region which contains antigen-presenting sites and carbohydrate-receptor binding regions, which is probably the region of the virus that binds to

target cells. The estimated mutation rate (1.21×10^{-2} to 1.41×10^{-2} substitutions per site per year) in this virus is high, even compared with other RNA viruses. Norovirus epidemics typically occur when groups of people spend time in close physical proximity to each other, such as on cruise ships, in hospitals, or in restaurants. People may remain infectious even after their diarrhea has ended. Norovirus is the cause of about 10% of cases in children.

The foundation of management of gastroenteritis, viral-caused or otherwise, is adequate hydration. For mild or moderate cases, this can be typically achieved via oral rehydration solution. For more severe cases, intravenous fluids may be needed. Gastroenteritis primarily affects children and those in the developing world.

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SECTION OVERVIEW

15.19: Fungal and Protozoan Diseases of the Digestive System

Topic hierarchy

15.19A: Ergot Poisoning

15.19B: Aflatoxin Poisoning

15.19C: Giardiasis

15.19D: Cryptosporidiosis

15.19E: Cyclospora Diarrheal Infection

15.19F: Amoebic Dysentery (Amoebiasis)

15.19G: Legionellosis

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15.19A: Ergot Poisoning

Ergot poisoning is caused by ingestion of the alkaloids produced by the ergot fungi.

Learning Objectives

- List the causes and effects of ergot poisoning

Key Points

- Ergot fungi typically infect rye, wheat and forage plants.
- Ingestion of the alkaloid toxins produced by the fungi can result in ergot poisoning in humans and foraging animals.
- Ergot poisoning can have either convulsive central nervous system effects or gangrenous symptoms caused by vasoconstriction effects.

Key Terms

- **alkaloids**: A class of organic heterocyclic bases.
- **gangrenous**: To be afflicted with gangrene.

Ergot poisoning is a type of illness associated with the ingestion of alkaloids produced by the fungi *Claviceps purpurea (C. purpurea)*. *Claviceps purpurea* is a fungus classified under the fungi genus *Claviceps*. This specific type of fungus is found on rye, and also on crops like wheat and barley. In addition, *Claviceps purpurea* can effect plants and crops that are typically considered forage plants. Thus, this type of fungus can also result in diseases within livestock.

The life cycle of *C. purpurea* begins when an ergot kernel, called a sclerotium, infects the host. The fungi continues to undergo proliferation and destroys the plant ovary. The first stage of ergot infection is a white soft tissue, called Sphacelia segetum, that drops out of the host. The white soft tissue contains asexual spores which infect additional host plants. This tissue, present within the host, is then converted into a hard Sclerotium clavus within the husk. At this specific stage, the alkaloids and lipids accumulate.



Figure: **Example of Ergot on Wheat**: This image shows ergot on a wheat spike.

The alkaloids, responsible for the ergot poisoning, are naturally occurring compounds that are mainly comprised of basic nitrogen atoms. Alkaloids are produced within various organisms as a secondary metabolite. Secondary metabolites are most commonly produced in plants as a defense system. The alkaloids produced by fungi are often toxic. Specifically, the alkaloid produced by *Claviceps purpurea* is ergoline based.

In cases of ergot poisoning (also known as ergotoxicosis or traditionally, Saint Anthony's Fire) alkaloids accumulate in the system due to the consumption of contaminated grain products. The symptoms which present in individuals with ergot poisoning can be classified as convulsive symptoms and gangrenous symptoms. The convulsive symptoms include seizures and effects on the central nervous system that range from hallucinations to psychotic episodes. The gangrenous symptoms are a result of vasoconstriction induced by the alkaloids. Peripheral systems, such as fingers and toes, are typically affected. More recently, ergot poisoning has been associated with an increased intake of ergot-based drugs. These drugs include those that promote vasoconstriction for treating migraines and Parkinson's disease.

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15.19B: Aflatoxin Poisoning

Aflatoxin poisoning is a result of ingestion of aflatoxins produced by *Aspergillus* that have contaminated a food source.

Learning Objectives

- Summarize the causes and effects of alfatoxin poisoning

Key Points

- Aspergillus flavus and Aspergillus parasiticus are two commonly known species of Aspergillus that can aflatoxin poisoning.
- Aflatoxin poisoning can result in either acute aflatoxicosis, which is a result of moderate to high level ingestion; or chronic aflatoxicosis, which results from ingestion of low to moderate levels of aflatoxins.
- Aspergillus species which cause aflatoxin poisoning are often found in crops in underdeveloped countries, due to lack of detection techniques and inadequate harvesting and storage.

Key Terms

- **mycotoxins**: a substance produced by a mold or fungus.

Aflatoxins are categorized as mycotoxins that are typically produced by species of *Aspergillus*. Aflatoxins, although only synthesized by a few *Aspergillus* species, are considered to be one of the most important mycotoxins identified to date. Both *Aspergillus flavus* and *Aspergillus parasiticus* are well known for their production of aflatoxins. Aflatoxins are most commonly transmitted to humans through the diet. Aflatoxins grow on whole grains and contaminate food supplies during processing, storage, or transport when there are favorable conditions for mold growth, specifically for the *Aspergillus* species.

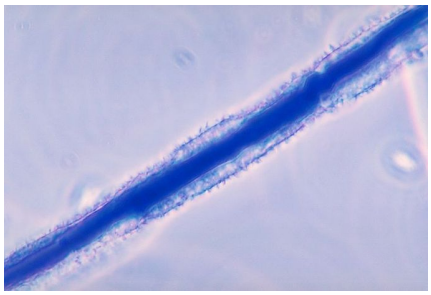

Figure: **Aspergillus flavus**: A species of Aspergillus that causes aflatoxin poisoning.

Aflatoxin poisoning, or aflatoxicosis, occurs when there is ingestion of aflatoxin contaminated foods. Upon ingestion or exposure to aflatoxin, it is common to see injury to the liver. Aflatoxicosis is a primarily hepatic disease, as the liver is the target organ for this toxin in mammals. Although the liver demonstrates the ability to metabolize the ingested aflatoxins, the intermediate formed is a reactive epoxide or a less harmful hydroxylated form referred to as M1. There have been various studies stating that metabolic activation of aflatoxins is required for the aflatoxin to exert its carcinogenic effects. These metabolites are harmful to the liver and have been implicated in liver cancer development. The aflatoxins produced by these *Aspergillus* species have been show to produce adducts (altered forms of DNA). These adducts are now used as a diagnostic factor to test for aflatoxin exposure by testing blood and urine.

Aflatoxin poisoning or aflatoxicosis is rarely diagnosed in developed countries but continues to be an issue in underdeveloped countries. In developed countries, commercial crops are screened for the presence of aflatoxins. However, in underdeveloped or developing countries, screening methods are lacking, or are in the process of being introduced. Interestingly, a rise in homegrown food has been correlated with a slight increase in aflatoxin exposure via diet.

Aflatoxin poisoning can be diagnosed as either acute or chronic. In cases of acute aflatoxicosis, an individual has been exposed to moderate to high levels of aflatoxins. Acute aflatoxicosis is characterized by symptoms such as hemorrhaging; acute liver damage and issues with digestion; and absorption and metabolism of nutrients. In cases of chronic aflatoxicosis, an individual has been exposed to low to moderate levels of aflatoxins. Chronic aflatoxicosis is characterized by symptoms such as dysfunctional food conversion and slow growth rates.

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15.19C: Giardiasis

Giardiasis, sometimes referred to as beaver fever, is caused by the protozoan Giardia lamblia and results in diarrheal illness.

Learning Objectives

- Summarize the life cycle and route of transmission for Giardia lamblia

Key Points

- Giardia lamblia is transmitted by exposure or ingestion of fecal contaminated sources such as soil, food, and water.
- Giardiasis is a common worldwide cause of gastroenteritis.
- The structure and life cycle of Giardia lamblia allow for survival in harsh environments and resistance against numerous types of disinfectants.

Key Terms

- **giardiasis**: an infectious diarrheal disease caused by the Giardia lamblia parasite
- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.
- **hematuria**: The presence of blood in the urine.

Giardiasis is a protozoan disease caused by *Giardia lamblia*. Giardiasis, referred to as beaver fever, is a common cause of gastroenteritis worldwide. The protozoa, *Giardia lamblia*, also referred to as *Giardia intestinalis* or *Giardia duodenalis*, infects humans via the fecal-oral route and is also suspected to be zoonotic. The organism is commonly found in soil, food, or water that has been contaminated with fecal matter from infected humans or animals. Beavers typically spread the parasite in their fecal matter in rivers and streams hence, giardiasis is commonly referred to as beaver fever. Individuals susceptible to infection by *Giardia lamblia* are those who come in frequent contact with individuals already infected. Travelers that spend time in wilderness area are at an increased risk due to ingestion of contaminated food or water sources and a lack of medical care or supplies.

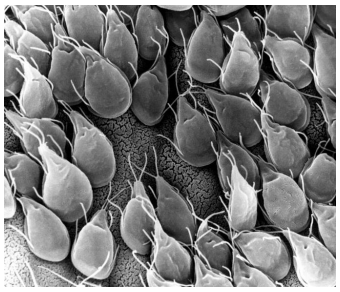

Figure: **Giardia infecting a small intestine**: A scanning electron micrograph of the surface of the small intestine of a gerbil infested with Giardia sp. protozoal, present in the trophozoite stage.

The life cycle, structure, and organization of *Giardia lamblia* promotes its survival for long periods of time outside the body. The organism itself is protected by an outer shell that provides protection against numerous harsh environments. In addition, the shell provides protection against disinfectants including chlorine. The cysts and trophozoites, found in the fecal matter, are extremely resistant to harsh environments. It is the cysts that are ingested and passed from exposure to contaminated food, water, or by the fecal-oral route. Once in the host, the trophozoites multiply via binary fission. They can either remain free within the lumen or attach to the mucosa by a sucking disk. Once the parasites move towards the colon, the encystation phase occurs and the cysts are infectious when passed in the stool.

Giardiasis is characterized as a disease of the gastrointestinal system. The symptoms include from fever, diarrhea, hematuria, stomach cramping, vomiting, flatulence, and loose stool. The symptoms are typically present one to two weeks post infection and can disappear and reappear cyclically. The pathogenecity of *Giardia lamblia* is characterized by its ability to coat the inside of the intestinal wall and inhibit nutrient absorption. The ability of the protozoan to block nutrient absorption can result in vitamin B12 deficiency. Additionally, a development of lactose intolerance is often associated with giardiasis infection.

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15.19D: Cryptosporidiosis

Learning Objectives

- Outline the life cycle of Cryptosporidium

Cryptosporidiosis is a type of parasitic disease caused by the parasite *Cryptosporidium*. Cryptosporidiosis is typically spread through the fecal-oral route and can be spread through contaminated water as well. Cryptosporiodiosis is one of most common waterborne diseases identified worldwide. The transmission of *Cryptosporidium* is based on successful ingestion of oocysts which are able to implant and infect the epithelial tissue of the intestine, hence, the gastrointestinal symptoms associated with cryptosporidiosis.

Cryptosporidium is classified as a protozoan within the Phylum Apicomplexa. Other pathogens classified in this phylum include the malaria parasite and the parasite that causes toxoplasmosis. The life cycle of *Cryptosporidium* allows for growth in a single host. The spore phase of the life cycle, also referred to as the oocyst stage, is the stage that allows survival of the pathogen in numerous harsh environments. The oocyst allows for survival against harsh chemicals including harsh disinfectants such as chlorine. The life cycle is characterized by the presence of both an asexual and sexual stage. The oocysts, once ingested, excyst within the small intestine and release sporozoites which attach to the microvilli. The sporozoites then develop into trophozoites and undergo asexual reproduction via schizogony. The trophozoites then develop into Type 1 and Type 2 merozoites which can either cause auto infection (Type 1) or undergo releasal and attach the epithelial cells (Type 2). Once released and attached, they will either develop in macrogamonts or microgamonts which correlate with male and female forms. Sexual reproduction occurs than zyogotes are developed. The zygote further develops into the oocyst which can either reinfect the host by rupturing and releasing sporozoites or be excreted into the environment.

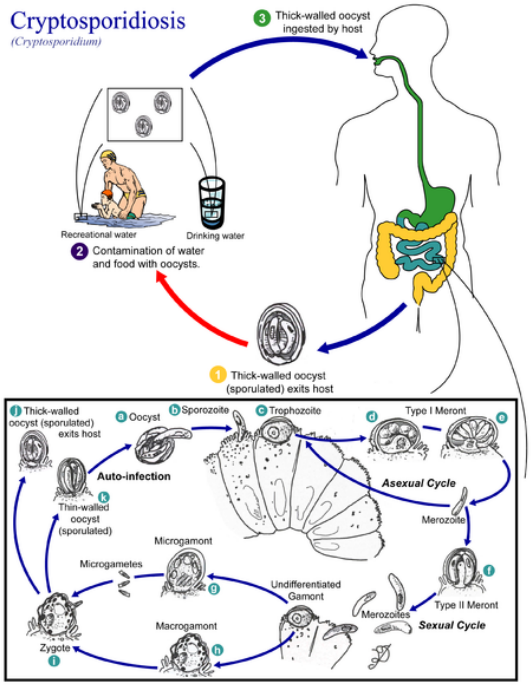

Figure: **Life cycle of Cryptosporidium**: An overview of the life cycle of Cryptosporidium.

The major symptom associated with individuals infected with *Cryptosporidium* is diarrhea. However, cryptosporidiosis is prevalent in immunocompromised individuals, such as those infected with the HIV virus. The symptoms of cryptosporidiosis in these cases are much more severe and can be fatal. The oocysts can initiate infections by attaching to the brush border of the small intestine and attacking the epithelial cells. Additional symptoms associated with cryptosporidiosis include abdominal cramping, malnutrition, weight loss, and nausea.

Key Points

- Cryptosporidium is commonly transmitted through food and water that has been contaminated with the feces of an infected individual.
- Cryptosporidium is commonly found in immunocompromised individuals that exhibit symptoms associated with this disease such as acute or persistent diarrhea.
- The life cycle of Cryptosporidium involves both asexual and sexual reproduction.

Key Terms

- **excyst**: The break down of a cyst wall.
- **schizogony**: A form of asexual reproduction in protozoans characterized by multiple divisions.

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15.19E: Cyclospora Diarrheal Infection

Cyclospora diarrheal infection is commonly referred to as traveler's diarrhea and is caused by the parasite Cyclospora cayetanensis.

Learning Objectives

- Outline the life cycle of Cyclospora cayetanensis

Key Points

- The life cycle of Cyclospora begins as the host ingests the oocyst form.
- Cyclospora is transmitted through fecal matter and is commonly found on contaminated fruits and vegetables in countries or areas with a lack of stringent health regulations.
- Cyclospora causes gastroenteritis with symptoms ranging from diarrhea to loss of appetite, weight loss, cramping, nausea and fatigue.

Key Terms

- **meronts**: After infecting a host cell, a trophozoite increases in size and during this process, the organism is referred to as a meront.
- **sporocysts**: a cysts that develops from a sporoblasts and results in the production of sporozoites.

Cyclospora diarrheal infection, commonly referred to as travelers diarrhea or cyclosporiasis, is caused by a specific species of *Cyclospora*. The protozoan that are categorized as cyclospora are defined by the spherical shape of the sporocysts. Specifically, *Cyclospora cayetanensis* is the species associated with the disease in both humans and primates. Cyclospora can be transmitted by consuming contaminated food or water. In 2012, cyclospora caused about 500 infections in 2012 in the US from a salad mix imported from Mexico and used in restaurants in Texas and Arkansas.

Life Cycle of Cyclospora

The life cycle of Cyclospora begins when the host is exposed and ingests the pathogen either in its oocyst or spore form. The oocyst is comprised of sporocytes which contain sporozoites. Upon release of the sporozoites, the epithelial cells of the intestine are penetrated. Within the intestinal cells, the sporozoites undergo multiple fission and develop into meronts which contain merozoites. The merozoites then undergo division and produce micro- and macro-gametes representing male and female gametes, respectively.

These gametes then reproduce and result in the formation of oocysts. It is the oocysts which pass through the intestinal tract and are released into the feces. The oocysts demonstrate the ability to undergo sporulation in a crop and water host as well beginning with the oocyst stage. It is during the oocyst stage that cyclospora exhibit a high resistance to disinfectants.

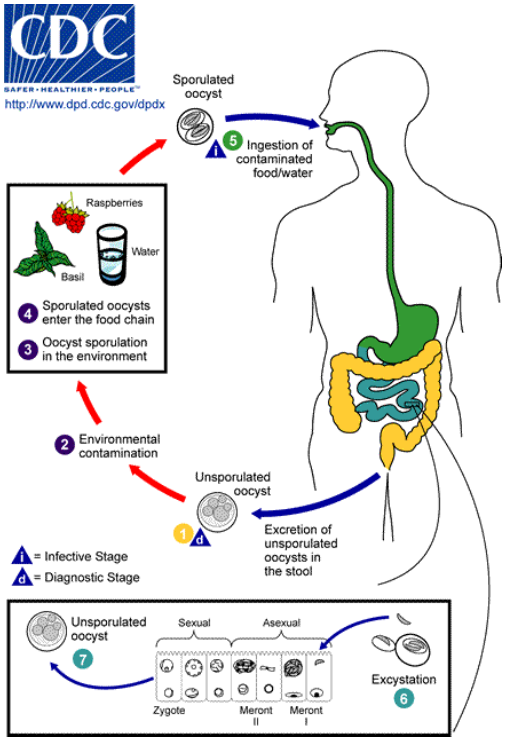

Figure: **Life cycle of cyclospora**: Cyclosporiasis (Cyclospora cayetanesis) When freshly passed in stools, the oocyst is not infective (1) (thus, direct fecal-oral transmission cannot occur; this differentiates Cyclospora from another important coccidian parasite, Cryptosporidium). In the environment (2), sporulation occurs after days or weeks at temperatures between 22°C to 32°C, resulting in division of the sporont into two sporocysts, each containing two elongate sporozoites (3). Fresh produce and water can serve as vehicles for transmission (4) and the sporulated oocysts are ingested (in contaminated food or water) (5). The oocysts excyst in the gastrointestinal tract, freeing the sporozoites which invade the epithelial cells of the small intestine (6). Inside the cells they undergo asexual multiplication and sexual development to mature into oocysts, which will be shed in stools (7). The potential mechanisms of contamination of food and water are still under investigation.

Symptoms of Cyclospora

The symptoms associated with this disease are categorized as gastroenteritis based issues. The symptoms range from watery, loose stool, weight loss, cramping, fatigue, vomiting, fever and nausea. The symptoms can be extremely severe if presented in an immunocompromised patient, such as a patient living with AIDS. The transmission of cyclospora to humans most often occurs by ingesting contaminated foods. In regions of the world where there is lack of health regulations, the chances of cyclospora exposure is increased. Often times, the contaminants include fresh fruits and vegetables which have been exposed to contaminated soil. Individuals exposed to these pathogens in these of regions are at high risk for developing cyclosporiasis, hence, the origin of the commonly known name, traveler's diarrhea.

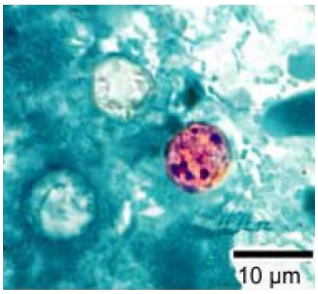

Figure: **Cyclospora cayetanensis oocysts**: A photomicrograph of oocysts from Cyclospora cayetanensis derived from a fresh stool sample.

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15.19F: Amoebic Dysentery (Amoebiasis)

Amoebic dysentery is caused by the parasite *Entamoeba histolytica* and infected individuals suffer from severe diarrhea, cramps, and fever.

Learning Objectives

- Outline the life cycle of Entamoeba histolytica

Key Points

- Amoebiasis is transmitted via food or water contaminated with fecal matter from an infected individual.
- The pathogen, Entamoeba histolytica, is mainly found in tropical areas and is protected from degradation and destruction by its protective shell, formed during its cyst stage.
- The cyst stage is typically passed in the feces and then ingested to cause infection.
- The amoebas are able to burrow into the walls of the intestines, causing damage.

Key Terms

- **trophozoites**: A protozoan in the feeding stage of its life cycle.

Amoebic dysentery, also referred to as amoebiasis, is caused by the ameoba *Entamoeba histolytica.* Dysentery is characterized as an inflammatory disorder of the intestine that results in severe diarrhea containing both mucus and blood in the feces, often accompanied with fever and abdominal pain.

The route of transmission for ameobic dysentery is the fecal-oral route. Transmission and infection occur upon exposure or ingestion of contaminated food and water. The infective cysts are passed via infected stool. The ameoba also demonstrates the ability to spread as free amoebae or trophozoites, meaning the cysts are not absolutely necessary; however, these states do not survive long outside of the host.

Ameobic dysentery is seen in both developing and industrialized countries, although it is most common in tropical areas. Ameobic cysts are often found in areas of the world where the use of human feces for fertilizer is common, often referred to as ‘night soil’. Upon ingestion of contaminated foods or water, the cysts will move into the intestinal area. These cysts are protected from stomach acids and are able to evade destruction. Once in the intestine, the cyst breaks open and releases the amoebas which then burrow into and damage the intestinal walls.

The amoebae or trophozoites are able to divide via binary fission and and produce cysts. If they are passed in the feces as is, instead of developing into cysts, their survival rate decreases as they are unable to survive in harsh environments. Interestingly, individuals can be asymptomatic if infected with trophozoites and can function as carriers by passing cysts in their stool.

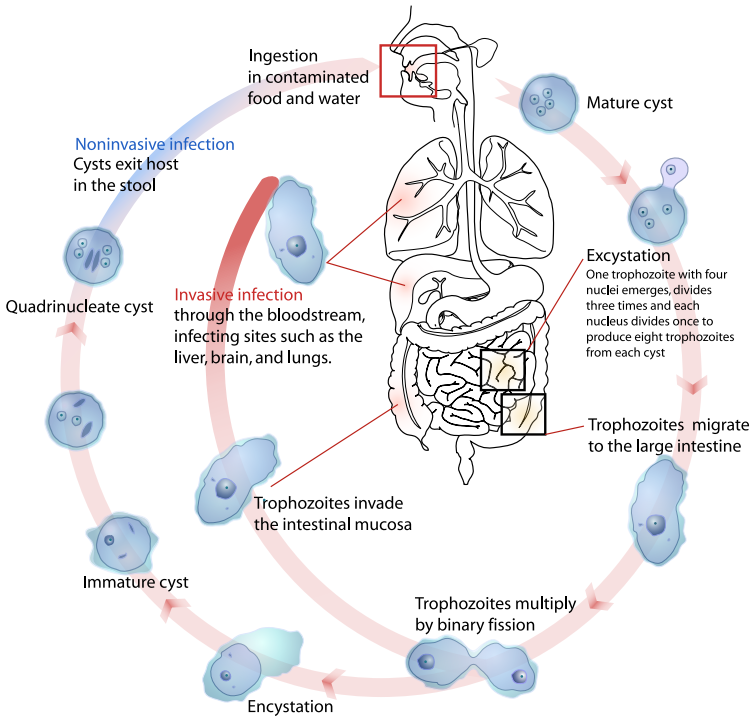

Figure: **Life Cycle of Entamoeba histolytica**: An overview of the life cycle of E. histolytica, the source of amoebic dysentery.

Symptoms of individuals infected with *Entamoeba histolytica* include ulcers, abdominal cramps, diarrhea, bloody stools, liquid stools, fever and vomiting.

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15.19G: Legionellosis

Legionellosis is most commonly caused by the Gram-negative bacteria *Legionella pneumophila* which is an aquatic organism.

Learning Objectives

- Discuss the mode of infection for the bacteria Legionella

Key Points

- Legionella pneumophila is an aquatic organism that is transmitted via aerosols.
- Legionellosis is caused by exposure to contaminated water sources including water towers, spas, fountains, swimming pools and cooling towers.
- Legionellosis-infected individuals have pneumonia -like symptoms with moderate to high fever ranges, chills and a dry cough.

Key Terms

- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **Legionnaire's disease**: The more severe form of legionellosis which produces high fever and pneumonia.

Legionellosis, commonly referred to as Legionnaire's disease, is caused by the pathogenic, gram-negative bacteria *Legionella*. It is characterized by flu- and pneumonia -like symptoms, including fevers and chills. In advanced stages of the disease, there are gastrointestinal and nervous system issues which result in diarrhea and nausea.

Legionella are a type of bacterium that reside within amoebae in the natural environment. The specific species most associated with legionellosis is *Legionella pneumophilia*, an aquatic organism. Legionella transmission occurs via aerosols and infection occurs when upon inhalation of the bacteria. After being inhaled, the bacteria infect the *macrophages* of the alveolar and exploit the host machinery to create an environment that promotes bacterial replication. However, the bacteria are not spread from one person to another. In the 1970s, the CDC investigated a large outbreak of legionellosis at Baptist Hospital that was spread through its air conditioner.



Figure: **Legionella pneumophila**: A microscopic image of Legionella pneumophila, the cause of Legionellosis.

Individuals infected with legionellosis have similar symptoms as those diagnosed with pneumonia. Symptoms include high fevers, chills, cough, muscle aches and headaches. For a diagnosis of legionellosis, x-rays and diagnostic tests are used to identify the bacteria. Individuals particularly at risk are older individuals, those immunocompromised or with chronic lung disease.

Legionellosis can take on two distinct forms commonly referred to as legion fever or pontiac fever. Legion fever resembles acute influenza and is the more severe form of the disease, characterized by high fever and pneumonia. Pontiac fever is a milder version and results in mild respiratory illness without the development of pneumonia.

Common sources of Legionella include swimming pools, cooling towers, hot-water systems such as spas, fountains, freshwater ponds and creeks. As seen, the major source for Legionella bacteria is infected water. The bacteria can become suspended in water droplets which are then inhaled into the lungs.

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SECTION OVERVIEW

15.2: Microbial Diseases of the Skin

Topic hierarchy

15.1A: Structure of the Skin: Epidermis

15.1B: Microbiota of the Skin

15.1C: Bacterial Skin Diseases

15.1D: Viral Skin Diseases

15.1E: Fungal Skin and Nail Diseases

15.1F: Parasitic Skin Diseases

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15.1A: Structure of the Skin: Epidermis

The epidermis includes five main layers: the stratum corneum, stratum lucidium, stratum granulosum, stratum spinosum, and stratum germinativum.

LEARNING OBJECTIVES

Describe the layers of the epidermis

KEY TAKEAWAYS

Key Points

- The epidermis provides a protective waterproof barrier that also keeps pathogens at bay and regulates body temperature.
- The main layers of the epidermis are: stratum corneum, stratum lucidium, stratum granulosm, stratum spinosum, stratum germinativum (also called stratum basale).
- Keratinocytes in the stratum basale proliferate during mitosis and the daughter cells move up the strata, changing shape and composition as they undergo multiple stages of cell differentiation.

Key Terms

- **keratinocyte**: the predominant cell type in the epidermis, the outermost layer of the skin, constituting 95% of the cells found there. Those keratinocytes found in the basal layer (stratum germinativum) of the skin are sometimes referred to as basal cells or basal keratinocytes.
- **stratum germinativum**: the basal layer—sometimes referred to as stratum basale—is the deepest of the five layers of the epidermis.
- **stratum corneum**: the most superficial layer of the epidermis from which dead skin sheds.
- **epidermis**: the outermost layer of skin.
- **stratum lucidum**: a layer of our skin that is found on the palms of our hands and the soles of our feet.

Layers of the Epidermis

The epidermis is the outermost layer of our skin. It is the layer we see with our eyes. It contains no blood supply of its own—which is why you can shave your skin and not cause any bleeding despite losing many cells in the process. Assuming, that is, you don't nick your skin to deep, where the blood supply is actually found. The epidermis is itself divided into at least four separate parts. A fifth part is present in some areas of our body. In order from the deepest layer of the epidermis to the most superficial, these layers (strata) are the:

- Stratum basale
- Stratum spinosum
- Stratum granulosum
- Stratum lucidum
- Stratum corneum

Stratum Basale

The stratum basale, also called the stratum germinativum, is the basal (base) layer of the epidermis. It is the layer that's closest to the blood supply lying underneath the epidermis.

This layer is one of the most important layers of our skin. This is because it contains the only cells of the epidermis that can divide via the process of mitosis, which means that skin cells germinate here, hence the word germinativum.

In this layer, the most numerous cells of the epidermis, called keratinocytes, arise thanks to mitosis. Keratinocytes produce the most important protein of the epidermis.

This protein is appropriately called keratin. Keratin makes our skin tough and provides us with much-needed protection from microorganisms, physical harm, and chemical irritation.

Millions of these new cells arise in the stratum basale on a daily basis. The newly produced cells push older cells into the upper layers of the epidermis with time. As these older cells move up toward the surface, they change their shape, nuclear, and chemical composition. These changes are, in part, what give the strata their unique characteristics.

Stratum Spinosum and Granulosum

From the stratum basale, the keratinocytes move into the stratum spinosum, a layer so called because its cells are spiny-shaped cells. The stratum spinosum is partly responsible for the skin's strength and flexibility. From there the keratinocytes move into the next layer, called the stratum granulosum. This layer gets its name from the fact that the cells located here contain many granules. The keratinocytes produce a lot of keratin in this layer—they become filled with keratin. This process is known as keratinization. The keratinocytes become flatter, more brittle, and lose their nuclei in the stratum granulosum as well.

Stratum Lucidum

Once the keratinocytes leave the stratum granulosum, they die and help form the stratum lucidum. This death occurs largely as a result of the distance the keratinocytes find themselves from the rich blood supply the cells of the stratum basale lie on top off. Devoid of nutrients and oxygen, the keratinocytes die as they are pushed towards the surface of our skin. The stratum lucidum is a layer that derives its name from the lucid (clear/transparent) appearance it gives off under a microscope. This layer is only easily found in certain hairless parts of our body, namely the palms of our hands and the soles of our feet. Meaning, the places where our skin is usually the thickest.

Stratum Corneum

From the stratum lucidum, the keratinocytes enter the next layer, called the stratum corneum (the horny layer filled with cornified cells). This the only layer of skin we see with our eyes. The keratinocytes in this layer are called corneocytes. They are devoid of almost all of their water and they are completely devoid of a nucleus at this point. They are dead skin cells filled with the tough protein keratin. In essence, they are a protein mass more so than they are a cell. The corneocytes serve as a hard protective layer against environmental trauma, such as abrasions, light, heat, chemicals, and microorganism. The cells of the stratum corneum are also surrounded by lipids (fats) that help repel water as well. These corneocytes are eventually shed into the environment and become part of the dandruff in our hair or the dust around us, which dust mites readily munch on. This entire cycle, from new keratinocyte in the straum basale to a dead cell flaked off into the air, takes between 25–45 days.

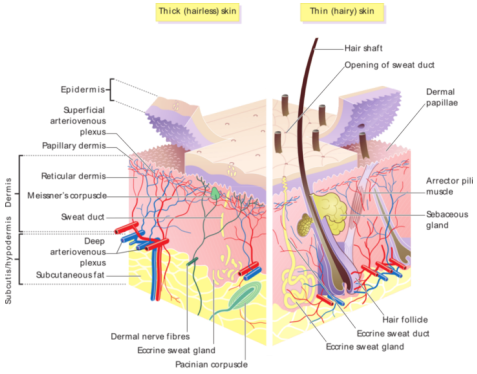

Figure: **Skin overview**: skin layers, of both hairy and hairless skin.

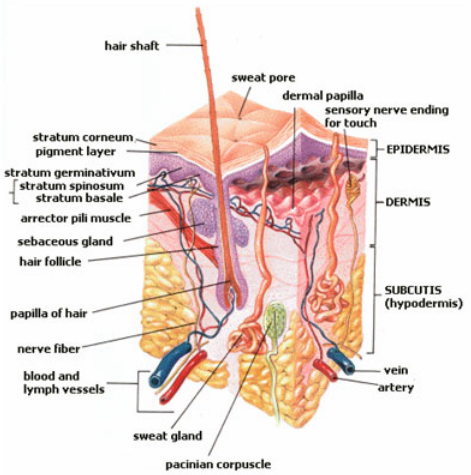

Figure: **Human skin**: This image details the parts of the integumentary system.

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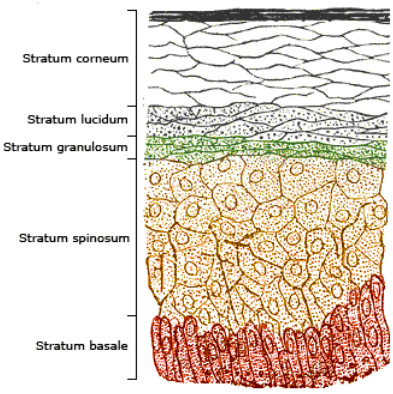

Layers of the epidermis: The epidermis is made up of 95% keratinocytes but also contains melanocytes, Langerhans cells, Merkel cells, and inflammatory cells. The stratum basale is primarily made up of basal keratinocyte cells, which can be considered the stem cells of the epidermis. They divide to form the keratinocytes of the stratum spinosum, which migrate superficially.

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15.1B: Microbiota of the Skin

The skin flora, more properly referred to as the skin microbiome or skin microbiota, are the microorganisms that reside on the skin.

Learning Objectives

- Describe the types of skin flora and how they can be beneficial for the organism

Key Points

- Most bacteria on the skin are found in the superficial layers of the epidermis and the upper parts of hair follicles.
- Skin flora are usually non-pathogenic, and either commensals (are not harmful to their host) or mutualistic (offer a benefit).
- The benefits bacteria can offer include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system.
- Resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people.

Key Terms

- **skin flora**: the skin flora, more properly referred to as the skin microbiome or skin microbiota, are the microorganisms which reside on the skin.
- **commensal**: a term for a form of symbiosis in which one organism derives a benefit while the other is unaffected
- **mutualistic**: mutually beneficial.

The skin flora, more properly referred to as the skin microbiome or skin microbiota, are the microorganisms that reside on the skin. Most bacteria on the skin are found in the superficial layers of the epidermis and the upper parts of hair follicles. Skin flora are usually non-pathogenic, and either commensals (are not harmful to their host) or mutualistic (offer a benefit). The benefits bacteria can offer include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system. However, resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people. Hygiene to control such flora is important in preventing the transmission of antibiotic resistant hospital-acquired infections.

A major nonhuman skin flora is Batrachochytrium dendrobatidis, a chytrid and non-hyphal zoosporic fungus that causes chytridiomycosis, an infectious disease thought to be responsible for the decline in amphibian populations. The estimate of the number of species present on skin bacteria has been radically changed by the use of 16S ribosomal RNA to identify bacterial species present on skin samples direct from their genetic material. Previously such identification had depended upon microbiological culture upon which many varieties of bacteria did not grow and so were hidden to science. Staphylococcus epidermidis and Staphylococcus aureus were thought from cultural based research to be dominant. However, 16S ribosomal RNA research found that while common these species make up only 5% of skin bacteria. However, skin variety provides a rich and diverse habitat for bacteria. Most come from four phyla: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%).

There are three main ecological areas for skin flora: sebaceous, moist, and dry. Propionibacteria and Staphylococci species are the main species in sebaceous areas. In moist places on the body Corynebacteria together with Staphylococci dominate. In dry areas, there is a mixture of species, but b-Proteobacteria and Flavobacteriales are dominant. Ecologically, sebaceous areas have greater species richness than moist and dry ones. The areas with least similarity between people in species are the spaces between fingers, the spaces between toes, axillae, and umbilical cord stump. Most similar are beside the nostril, nares (inside the nostril), and on the back.

Skin microflora can be commensals, mutualistic, or pathogens. Often they can be all three depending upon the strength of the person's immune system. Research on the immune system in the gut and lungs has shown that microflora aids immunity development. However, such research has only started upon whether this is the case with the skin. Pseudomonas aeruginosa is an example of a mutualistic bacterium that can turn into a pathogen and cause disease. If it gains entry into the blood system it can result in infections in bone, joint, gastrointestinal, and respiratory systems and it can also cause dermatitis. However,

Pseudomonas aeruginosa produces antimicrobial substances such as pseudomonic acid (that are exploited commercially such as Mupirocin). This works against staphylococcal and streptococcal infections. Pseudomonas aeruginosa also produces substances that inhibit the growth of fungus species such as Candida krusei, Candida albicans, Torulopsis glabrata, Saccharomyces cerevisiae,

and Aspergillus fumigatus. It can also inhibit the growth of Helicobacter pylori. Fatty acids (caproic acid) on the skin inhibit bacteria, especially after puberty, when undecylic acid becomes the primary fatty acid on the skin. Undecylic acid provides resistance to ringworm fungus and other skin infections.

Another aspect of bacteria is the generation of body odor. Sweat is odorless. However, several bacteria may consume it and create byproducts which may be considered putrid by man (as in contrast to flies, for example, that may find them attractive/appealing). For example, Propionibacteria in adolescent and adult produce propionic acid in sebaceous glands.

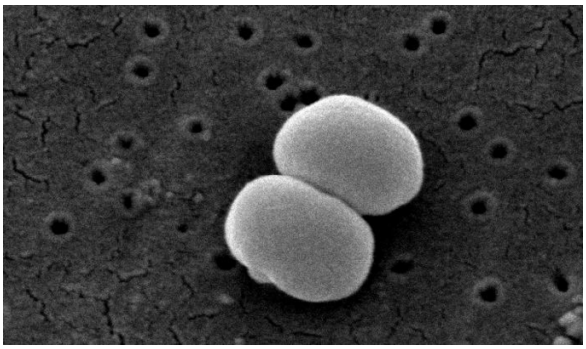

Figure: **Staphylococcus epidermidis**: Scanning electron microscope image of Staphylococcus epidermidis one of roughly 1,000 bacteria species present on human skin. Though usually not pathogenic, it can cause skin infections and even life threatening illnesses in those that are immunocompromised.

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15.1C: Bacterial Skin Diseases

Bacterial skin infections include impetigo, erysipelas, and cellulitis.

LEARNING OBJECTIVES

Describe how impetigo, erysipelas and cellulitis are acquired and the treatment options available

KEY TAKEAWAYS

Key Points

- Impetigo is a highly contagious bacterial skin infection most common among pre-school children primarily caused by Staphylococcus aureus and sometimes by Streptococcus pyogenes.
- Erysipelas is an acute streptococcus bacterial infection of the upper dermis and superficial lymphatics.
- Cellulitis is a diffuse inflammation of connective tissue with severe inflammation of dermal and subcutaneous layers of the skin.
- Antimicrobial therapy is available for impetigo, erysipelas, and cellulitis.

Key Terms

- **erysipelas**: a severe skin disease caused by streptococcus infection in surface and surrounding tissue, marked by continued spreading inflammation
- **impetigo**: a contagious bacterial skin disease forming pustules and yellow crusty sores, chiefly on the face and hands. It is common in children. Infection is often through cuts or insect bites.
- **cellulitis**: an inflammation of subcutaneous or connective tissue caused by a bacterial infection



Figure: Facial impetigo.

Common Bacterial Skin Infections

Bacterial skin infections include impetigo, erysipelas, and cellulitis.

IMPETIGO

Impetigo is a highly contagious bacterial skin infection most common among pre-school children. It is primarily caused by Staphylococcus aureus and sometimes by Streptococcus pyogenes. The infection is spread by direct contact with lesions or with nasal carriers. The incubation period is 1–3 days. Dried streptococci in the air are not infectious to intact skin. Scratching may spread the lesions. Impetigo generally appears as honey-colored scabs formed from dried serum and is often found on the arms, legs, or face . For generations, the disease was treated with an application of the antiseptic *gentian violet*. Today, topical or oral antibiotics are usually prescribed.



Figure: **Facial erysipelas**. Erysipelas of the face due to invasive Streptococcus.

ERYSIPELAS

Erysipelas is an acute streptococcus bacterial infection of the upper dermis and superficial lymphatics. This disease is most common among the elderly, infants, and children. People with immune deficiency, diabetes, alcoholism, skin ulceration, fungal infections, and impaired lymphatic drainage (e.g., after mastectomy, pelvic surgery, bypass grafting) are also at increased risk. Patients typically develop symptoms including high fevers, shaking, chills, fatigue, headaches, vomiting, and general illness within 48 hours of the initial infection. The erythematous skin lesion enlarges rapidly and has a sharply demarcated raised edge. It appears as a red, swollen, warm, hardened and painful rash, similar in consistency to an orange peel. More severe infections can result in vesicles, bullae, and petechiae, with possible skin necrosis. Lymph nodes may be swollen and lymphedema may occur. Occasionally, a red streak extending to the lymph node can be seen. Most cases of erysipelas are due to Streptococcus pyogenes (also known as beta-hemolytic group A streptococci), although non-group A streptococci can also be the causative agent. Beta-hemolytic, non-group A streptococci include Streptococcus agalactiae, also known as group B strep or GBS. Depending on the severity, treatment involves either oral or intravenous antibiotics, using penicillins, clindamycin, or erythromycin. While illness symptoms resolve in a day or two, the skin may take weeks to return to normal.



Figure: **Cellulitis**. Left shin infected with cellulitis.

CELLULITIS

Cellulitis is a diffuse inflammation of connective tissue with severe inflammation of dermal and subcutaneous layers of the skin. Cellulitis can be caused by normal skin flora or by exogenous bacteria, and often occurs where the skin has previously been broken. Common points of infection include cracks in the skin, cuts, blisters, burns, insect bites, surgical wounds, intravenous drug injection, or sites of intravenous catheter insertion. Group A Streptococcus and Staphylococcus are the most common of these bacteria, which are part of the normal flora of the skin, but normally cause no actual infection while on the skin's outer surface. Skin on the face or lower legs is most commonly affected by this infection, though cellulitis can occur on any part of the body. The mainstay of therapy remains treatment with appropriate antibiotics Recovery periods last from 48 hours to six months. The typical signature symptom of cellulitis is an area which is red, hot, and tender . Cellulitis is most often a clinical diagnosis, and local

cultures do not always identify the causative organism. Blood cultures usually are positive only if the patient develops generalized sepsis.Treatment consists of resting the affected area, cutting away dead tissue, and administration of antibiotics (either oral or intravenous).

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15.1D: Viral Skin Diseases

Virus-related cutaneous conditions include cold sores, shingles, and warts.

Learning Objectives

- Describe what causes cold sores, shingles and warts and the treatment options available

Key Points

- Oral herpes, the visible symptoms of which are colloquially called cold sores or fever blisters, is an infection of the face or mouth and is the most common form of infection by herpes simplex.
- Herpes zoster (or simply zoster), commonly known as shingles, is a viral disease caused by reactivation of latent varizella zoster virus and characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe.
- A wart is generally a small, rough growth, typically on a human's hands or feet that can resemble a cauliflower or a solid blister and it is caused by infection by the human papilloma virus.

Key Terms

- **shingles**: a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe
- **wart**: a type of deformed growth occurring on the skin caused by the human papillomavirus (HPV).
- **cold sore**: a small bump on the lips resulting from infection by the herpes virus.
- **zoster**: the disease called herpes zoster (from the typically beltlike pattern of its rash); shingles.

Virus-related cutaneous conditions are caused by two main groups of viruses–DNA and RNA types–both of which are obligatory intracellular parasites.

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses. While only a small number of skin diseases account for most visits to the physician, thousands of skin conditions have been described. Three common skin conditions that result from viral infections are cold sores, shingles, and warts.

Herpes

Herpes simplex is a viral disease from the herpesviridae family caused by both Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Infection with the herpes virus is categorized into one of several distinct disorders based on the site of infection. Oral herpes , the visible symptoms of which are colloquially called cold sores or fever blisters, is an infection of the face or mouth and is the most common form of infection. Genital herpes, known simply as herpes, is the second most common form of herpes. Herpes simplex is most easily transmitted by direct contact with a lesion or the body fluid of an infected individual. Transmission may also occur through skin-to-skin contact during periods of asymptomatic shedding. Barrier protection methods are the most reliable method of preventing transmission of herpes, but they merely reduce rather than eliminate risk. Oral herpes is easily diagnosed if the patient presents with visible sores or ulcers. Once infected, the virus remains in the body for life. Recurrent infections (outbreaks) may occur from time to time, especially in times of immune impairment such as HIV and cancer-related immune suppression. However, after several years, outbreaks become less severe and more sporadic, and some people will become perpetually asymptomatic and will no longer experience outbreaks, though they may still be contagious to others. Treatments with antivirals can reduce viral shedding and alleviate the severity of symptomatic episodes.

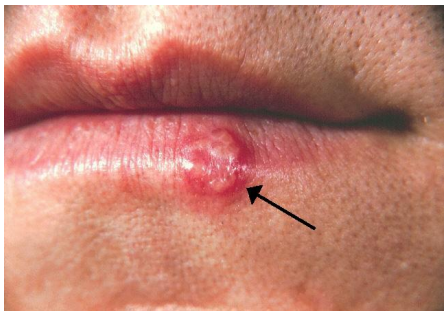

Figure: **Herpes simplex**. Herpes labialis or cold sore of the lower lip. Note the blisters in a group marked by an arrow.

Herpes Zoster

Herpes zoster (or simply zoster), commonly known as shingles, is a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe. The initial infection with varicella zoster virus (VZV) causes the acute (short-lived) illness chickenpox which generally occurs in children and young people. Once an episode of chickenpox has resolved, the virus is not eliminated from the body but remains latent and can go on to cause shingles—an illness with very different symptoms—often many years after the initial infection. Although the zoster rash usually heals within two to four weeks, some sufferers experience residual nerve pain for months or years, a condition called postherpetic neuralgia. Exactly how the virus remains latent in the body, and subsequently re-activates is not understood. The earliest symptoms of herpes zoster, which include headache, fever, and malaise, are nonspecific, and may result in an incorrect diagnosis. In most cases after 1–2 days, but sometimes as long as three weeks, the initial phase is followed by the appearance of the characteristic skin rash. The pain and rash most commonly occurs on the torso, but can appear on the face, eyes, or other parts of the body.

At first the rash appears similar to the first appearance of hives. However, unlike hives, herpes zoster causes skin changes limited to a dermatome, normally resulting in a stripe or belt-like pattern that is limited to one side of the body and does not cross the midline. The goals of treatment are to limit the severity and duration of pain, shorten the duration of a shingles episode, and reduce complications. Symptomatic treatment is often needed for the complication of postherpetic neuralgia. Topical lotions containing calamine can be used on the rash or blisters and may be soothing. Antiviral drugs inhibit VZV replication and reduce the severity and duration of herpes zoster with minimal side effects, but do not reliably prevent postherpetic neuralgia. Of these drugs, acyclovir has been the standard treatment.



Figure: **Herpes Zoster**. Neck Herpes zoster blisters on the neck and shoulder.

A wart is generally a small, rough growth, typically on a human’s hands or feet , but often other locations, that can resemble a cauliflower or a solid blister. They are caused by a viral infection, specifically by one of the many types of human papillomavirus (HPV). It is possible to get warts from others. They are contagious and usually enter the body in an area of broken skin. They typically disappear after a few months but can last for years and can recur. Gardasil is an HPV vaccine aimed at preventing cervical cancers and genital warts. There are many treatments and procedures associated with wart removal.



Figure: Warts. Warts on the big toe.

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15.1E: Fungal Skin and Nail Diseases

Common fungal skin diseases include athlete's foot, jock itch, and ringworm.

Learning Objectives

- Describe how fungal skin and nail diseases arise, their characteristic symptoms and the treatment options available

Key Points

- Athlete's foot (also known as ringworm of the foot and tinea pedis) is an infection of the skin that causes scaling, flaking, and itching of affected areas and is caused by a fungi in the genus Trichophyton.
- Tinea cruris, also known as jock itch, is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males.
- Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle.

Key Terms

- **jock itch**: a fungal infection, tinea cruris, of the groin region, due to the fungus Trichophyton rubrum and others.
- **ringworm**: a contagious fungal affliction of the skin, characterized by ring-shaped discoloured patches, covered by vesicles or scales.
- **athlete's foot**: a fungal infection of the skin of the foot, usually between the toes, caused by the pathogen fungi. Scientific name: tinea pedis.

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common fungal skin and nail diseases include athlete's foot, jock itch, and ringworm.

Athlete's foot (also known as ringworm of the foot and tinea pedis;) is an infection of the skin that is caused by a fungi in the genus Trichophyton. While it is typically transmitted in moist communal areas where people walk barefoot, the disease requires a warm moist environment, such as the inside of a shoe, in order to incubate. Athlete's foot causes scaling, flaking, and itching of the affected skin. Blisters and cracked skin may also occur, leading to exposed raw tissue, pain, swelling, and inflammation. Secondary bacterial infection can accompany the fungal infection, sometimes requiring a course of oral antibiotics. Athlete's foot can usually be diagnosed by visual inspection of the skin, but where the diagnosis is in doubt direct microscopy of a potassium hydroxide preparation (known as a KOH test) may help rule out other possible causes, such as eczema or psoriasis. Without medication athlete's foot resolves in 30–40% of cases and topical antifungal medication consistently produce much higher percentages of a cure. Conventional treatment typically involves daily or twice daily application of a topical medication in conjunction with hygiene measures outlined in the above section on prevention. Keeping feet dry and practicing good hygiene is crucial to preventing reinfection. Severe or prolonged fungal skin infections may require treatment with oral antifungal medication.



Figure: **Athlete's Foot**. A severe case of athlete's foot.

Tinea cruris, also known as crotch itch, crotch rot, Dhobie itch, eczema marginatum, gym itch, jock itch, jock rot, and ringworm of the groin is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males. As the common name for this condition implies, it causes itching or a burning sensation in the groin area, thigh skin folds, or anus. It may involve the

inner thighs and genital areas, as well as extending back to the perineum and perianal areas. Affected areas may appear red, tan, or brown, with flaking, rippling, peeling, or cracking skin. Opportunistic infections (infections that are caused by a diminished immune system) are frequent. Fungus from other parts of the body (commonly tinea pedis or 'athlete's foot') can contribute to this itch. A warm, damp environment allowing the fungus to cultivate greatly contributes; especially with tight, sweaty, or rubbing clothing such as a jockstrap. Medical professionals suggest keeping the groin area clean and dry by drying off thoroughly after bathing and putting on dry clothing right away after swimming or perspiring. Other recommendations to prevent this infection are: not sharing clothing or towels with others, showering immediately after athletic activities, wearing loose cotton underwear, avoiding tight-fitting clothes, and using antifungal powders. Tinea cruris is best treated with topical antifungal medications of the allylamine or azole type.

Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle. The term "ringworm" is a misnomer, since the condition is caused by fungi of several different species and not by parasitic worms. The fungi that cause parasitic infection (dermatophytes) feed on keratin, the material found in the outer layer of skin, hair, and nails. These fungi thrive on skin that is warm and moist, but may also survive directly on the outsides of hair shafts or in their interiors. In pets, the fungus responsible for the disease survives in skin and on the outer surface of hairs. Advice often given to prevent this infection includes: avoiding sharing clothing, sports equipment, towels, or sheets and washing clothes in hot water with fungicidal soap after suspected exposure to ringworm. After being exposed to places where the potential of being infected is high, one should wash with an antibacterial and anti-fungal soap or one that contains tea tree oil, which contains terpinen-4-ol. Antifungal treatments include topical agents such as miconazole, terbinafine, clotrimazole, ketoconazole, or tolnaftate applied twice daily until symptoms resolve — usually within one or two weeks

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15.1F: Parasitic Skin Diseases

Learning Objectives

- Describe how the parasitic skin infections creeping eruption, lice and scabies arise and the treatment options available

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. The major function of this system is as a barrier against the external environment. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common parasitic skin diseases include creeping eruption, lice, and scabies.

Cutaneous larva migrans (abbreviated CLM) is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae). The most common species that cayse this disease in the Americas is Ancylostoma braziliense. Colloquially called creeping eruption due to the way it looks, the disease is also somewhat ambiguously known as “ground itch” or (in some parts of the southern U.S.) “sandworms,” as the larvae like to live in sandy soil. Another vernacular name is plumber’s itch. The medical term CLM literally means “wandering larvae in the skin. ” These parasites are found in dog and cat feces and although they are able to infect the deeper tissues of these animals (through to the lungs and then the intestinal tract), in humans they are only able to penetrate the outer layers of the skin and thus create the typical wormlike burrows visible underneath the skin . The parasites apparently lack the collagenase enzymes required to penetrate through the basement membrane deeper into the skin. The infection causes a red, intense itching eruption. The itching can become very painful and if scratched may allow a secondary bacterial infection to develop but it will stop after the parasites are dead. Systemic (oral) agents to treat this infection include albendazole (trade name Albenza) and ivermectin (trade name Stromectol).



Figure: **Larva Migrans Cutanea**. Typical “creeping eruption” associated with cutaneous larva migrans.

Louse (plural: lice) is the common name for members of over 3,000 species of wingless insects of the order Phthiraptera, three of which are classified as human disease agents. They are obligate ectoparasites of every avian and mammalian order except for monotremes (the platypus and echidnas), bats, whales, dolphins, porpoises, and pangolins. Most lice are scavengers, feeding on skin and other debris found on the host’s body, but some species feed on sebaceous secretions and blood. Most are found only on specific types of animals, and, in some cases, only to a particular part of the body. Some animals are known to host up to 15 different species, although one to three is typical for mammals, and two to six for birds. For example, in humans, different species of louse inhabit the scalp and pubic hair. Lice generally cannot survive for long if removed from their host. Humans host three different kinds of lice: head lice, body lice, and pubic lice. Lice infestations can be controlled with lice combs and medicated shampoos or washes.

Scabies (from Latin: scabere, “to scratch”), known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals. The disease may be transmitted from objects, but is most often transmitted by direct skin-to-skin contact, with a higher risk with prolonged contact. Initial infections require four to six weeks to become symptomatic. Reinfection, however, may manifest symptoms within as little as 24 hours. Because the symptoms are allergic, their delay in onset is often mirrored by a significant delay in relief after the parasites have been eradicated. The characteristic symptoms of a scabies infection include intense itching and superficial burrows . The burrow tracks are often linear, to the point that a neat “line” of four or more closely placed and equally developed mosquito-like “bites” is almost diagnostic of the disease. Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or there is

itchiness of another household member. The classical sign of scabies is the burrows made by the mites within the skin. To detect the burrow, the suspected area is rubbed with ink from a fountain pen or a topical tetracycline solution, which glows under a special light. A number of medications are effective in treating scabies with permethrin being the most effective treatment. However, treatment must often involve the entire household or community to prevent re-infection. Options to improve itchiness include antihistamines.



Figure: **Acarodermatitis**. Scabies of the foot.

Key Points

- Cutaneous larva migrans is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae) and characterized by a red, intense itching eruption.
- Humans host three different kinds of lice (head lice, body lice, and pubic lice). Lice infestations can be controlled with lice combs and medicated shampoos or washes.
- Scabies, known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals.

Key Terms

- **scabies**: an infestation of parasitic mites, Sarcoptes scabiei, causing intense itching caused by the mites burrowing into the skin of humans and other animals. It is easily transmissible from human to human; secondary skin infection may occur.
- **cutaneous larva migrans**: a skin disease in humans, caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae).
- **louse**: a small parasitic wingless insect of the order Phthiraptera.

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SECTION OVERVIEW

15.20: Helminthic Diseases of the Digestive System

Topic hierarchy

15.20A: Tapeworms

15.20B: Hydatid Disease

15.20C: Nematodes

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15.20A: Tapeworms

Learning Objectives

- Compare and contrast the routes of transmission for various tapeworms and describe their life cycles

Tapeworms are characterized as adult parasitic flatworms that target and infect the digestive tract. Typically, transmission occurs by ingestion of a live tapeworm larva which is found in undercooked or contaminated food. Once inside the digestive tract, the larvae can then grow and develop into a large tapeworm. There are various types of tapeworms identified to date that are capable of infecting humans. A few common tapeworms include the pork tapeworm (*Taenia solium*), the beef tapeworm (*Taenia saginata*), and the fish tapeworm (*Diphyllobothrium spp*.).

Taenia solium

Taenia solium, the pork tapeworm, infects both pigs and humans. Humans are typically infected by ingesting infected pork. *Taenia solium* will target the intestinal area in humans. Using the four suckers and two rows of hooks present on its scolex, it lodges itself against the intestinal wall. Once anchored, the tapeworm continues to grow in the intestine and will pass its eggs through the feces. When *Taenia solium* is in its larval stage, it is referred to as a cysticercus and can cause cysticercosis. Cysticercosis occurs when the cysticerci reach the central nervous system and cause neurological issues.



Figure: ***Scolex of the Taenia solium****: An image of the scolex of the Taenia solium.*

Taenia saginata

Taenia saginata, the beef tapeworm, is capable of infecting both cattle and humans. Infection by *Taenia saginata* is referred to as taeniasis in humans and occurs by ingestion of contaminated meat that has been improperly handled. Taeniasis is caused by the ability of the tapeworm to lodge itself in the small intestine of the human and release fertilized eggs through the feces. The eggs can then infect cattle upon ingestion. Upon infection of the cattle, the fertilized eggs will develop into zygotes which will exit the digestive tract and enter into the circulatory system. The larval stages will then form cysts, referred to as Cysticercus bovis, within the muscular system of the cattle. Therefore, if humans ingest under prepared meat with cysts, the cysts will break open into the digestive system and develop into an adult tapeworm in the human host.

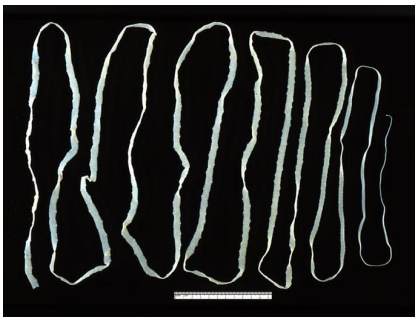

Figure: ***Tapeworm****: An adult Taenia saginata.*

Diphyllobothrium spp.

Diphyllobothrium spp, the fish tapeworm, encompasses various species that can infect humans upon ingestion of under cooked or raw fish. For example, these tapeworms include those found on broad fish and salmon. Interestingly, only a few species of these tapeworms are found to infect humans on a frequent basis. The tapeworms found in fish exhibit the ability to also infect canines, felines, bears, and mussels.

The life cycle for fish tapeworms includes movement through numerous hosts. The mammal host is considered the definitive host as this is the site of worm reproduction. The immature eggs are passed through the feces of the mammal host and then infect a freshwater host. This freshwater host is considered to be the intermediate host. The intermediate host is then ingested by a second intermediate host which includes the fish. The larvae, which developed in the first intermediate host, then migrate out into the flesh of the fish (the second intermediate host). The larvae develop into a more mature form and constitute the infective stage for the definitive host. It is important to note that many second intermediate hosts are ingested by larger predator species that are utilized as a food source for humans. Therefore, it is not necessary for humans to directly eat the second intermediate host in order to be infected.

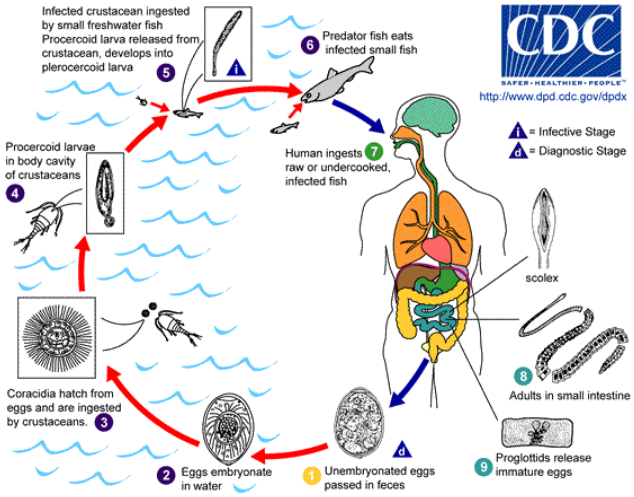

Figure: ***Diphylloborthrium latum life cycle****: Overview of the life cycle of Diphylloborthrium latum. Note the various hosts which are necessary for successful transmission.*

Key Points

- There are numerous types of tapeworms capable of infecting humans including beef, pork, and fish tapeworms.
- Taenia solium, the pork tapeworm, are passed via infected feces to the pig host but requires ingestion of under cooked pork by a human to ensure transmission.
- Taenia saginata, the beef tapeworm, are passed to humans by ingesting under cooked or raw beef that has been infected with the cyst stage in the life cycle.
- Diphyllobothrium spp, the fish tapeworm, requires multiple hosts to successfully infect a human host.

Key Terms

- **scolex**: The “head” of the tapeworm that contains suckers and rows of hooks by which it attaches itself to the host.

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15.20B: Hydatid Disease

Learning Objectives

- Outline the life cycle of Echinococcus granulosus

Hydatid disease, commonly referred to as echinococcosis, is a result of infection by the tapeworm included in the *Echinococcus spp*. *Echinococcus multilocularis* results in alveolar echinococcosis and *Echinococcus vogeli* can cause polycystic echinococcosis. In individuals that develop alveolar echinococcosis, which is extremely rare, cysts develop and grow within the alveolar, liver, lungs, and brain. In the cases of alveolar echinococcosis, the parasite responsible, *Echinococcus multilocularis*, is associated with dogs, cats, wolves and most commonly, foxes, serving as the definitive hosts. The intermediate hosts include small rodents. In individuals that develop polycystic echinococcosis, there is the development of slow growing cysts within the body that exhibit the capability to infiltrate surrounding areas. Cysts are typically found in the liver and in the thorax or abdominal cavity. The parasite responsible for polycystic echinococcosis, *Echinococcus vogeli*, uses dogs or bush dogs as a definitive host and rodents as an intermediate hosts.

Echinococcus granulosus is a tapeworm found in dogs, who function as the definitive host, as well as sheep, cattle, goats, and pigs who serve as intermediate hosts. *Echinococcus granulosus* are capable of infecting humans, resulting in hydatid disease, and cause slowly enlarging cysts that develop in vital organs such as the liver or lungs, also referred to as cystic echinococcosis. However, the growth of these cysts are slow and may go unnoticed for a significant duration of time. This form of echinococcosis is more prevalent and commonly found in humans. The adult *Echinococcus granulosus* targets the small bowel of the definitive hosts and release eggs through the feces. After ingestion by the intermediate hosts, the eggs will hatch and penetrate the intestinal wall. The exiting of the intestinal wall results in circulation of oncospheres that will target various organs, including the liver and lungs. The oncospheres undergo further growth and form cysts. The definitive host will then become infected upon ingestion of the cyst-containing organs of the infected intermediate host. It is within the definitive host that the cyst will develop into the adult stage and the cycle continues and repeats.

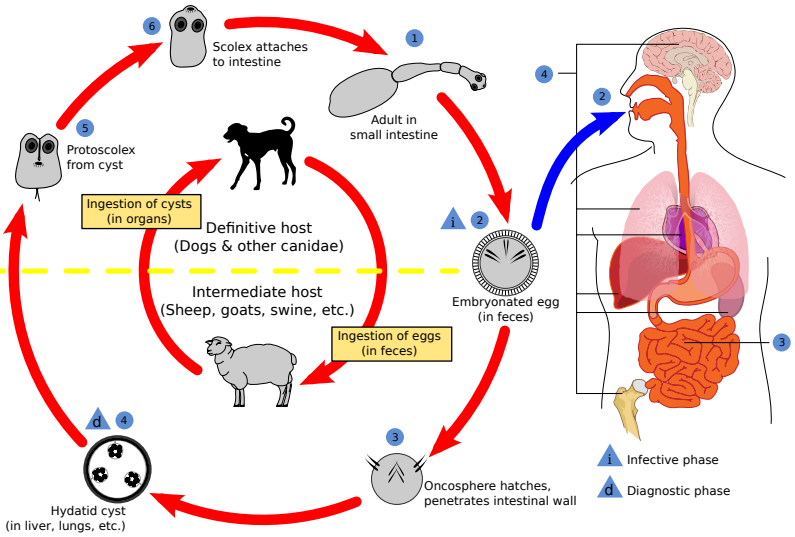

Figure: ***Overview of the Echinococcus life cycle****: A general overview of the various hosts and steps involved in the life cycle of Echinococcus species.*

Hydatid disease is characterized by the growth of these cysts into the adult stage for the tapeworm. Individuals infected with Echinococcus species that develop hydatid disease may not develop symptoms for many years after infection. However, if symptoms develop, it may present in the form of pain or discomfort due to the growing cysts in the upper abdominal regions. Additionally, rupture of fluid within the cysts can result in various medical issues including allergic reactions or death.

Key Points

- *Echinococcus granulosus* causes hydatid disease, or cystic echinococcus and causes slowly enlarging cysts to develop in vital organs.

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- *Echinococcus multilocularis* results in alveolar echinococcosis and *Echinococcus vogeli* can cause polycystic echinococcosis.
- Individuals infected with *Echinococcus* species who develop hydatid disease may not develop symptoms for many years after infection.

Key Terms

- **echinococcosis**: a parasitic disease of both animals and humans, also known as hydatid disease.

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15.20C: Nematodes

Learning Objectives

- Compare and contrast mechanisms of infection for the parasitic nematodes: *Ascaris lumbricoides* and *Enterobius*

Nematodes, or roundworms, are the most diverse phylum of pseudocoelomates and one of the most diverse animal phyla. Nematodes are characterized by the presence of a tubular digestive system with openings at both ends. They can be found in various ecosystems ranging from the polar regions to the tropics, fresh to marine water and various terrestrial environments ranging from mountains, deserts and oceanic floors. Nematodes are also capable of exhibiting parasitic behavior that contribute to digestive system diseases. Analysis of parasitic nematodes reveals the presence of specific body structures which promote parasitic behaviors such as ridges, rings or bristles that allow for attachment. Parasitic nematodes that commonly infect humans include ascarids (*Ascaris*), pinworms (*Enterobius*), whipworms (*Trichuris trichiura*), filarias and hookworms. The following is a brief overview of two of these types of roundworms, including *Ascaris* and *Enterobious*.

Ascariasis

Ascariasis is a disease that is caused by the parasitic roundworm *Ascaris lumbricoides.* Ascariasis is commonly found in tropical and sub-tropical regions and is transmitted by ingesting food contaminated with *Ascaris* eggs that are typically present in the feces of an infected individual. Upon ingestion of *Ascaris* eggs, the larvae continue development and hatch within the intestine of the host. The larvae burrow through the intestinal wall and begin circulation in the system and migrate to the lungs. Once they have migrated to the lungs, the larvae break into the alveoli and continue to move through the trachea and esophagus where they are eventually coughed up and swallowed. For a second time, the larvae enter into the intestine and mature into adult worms. Individuals affected with ascariasis can be asymptomatic or suffer from visceral damage due to the travel of the larvae through the body. The presence of the worms within the intestine may also result in malabsorption or intestinal blockage.

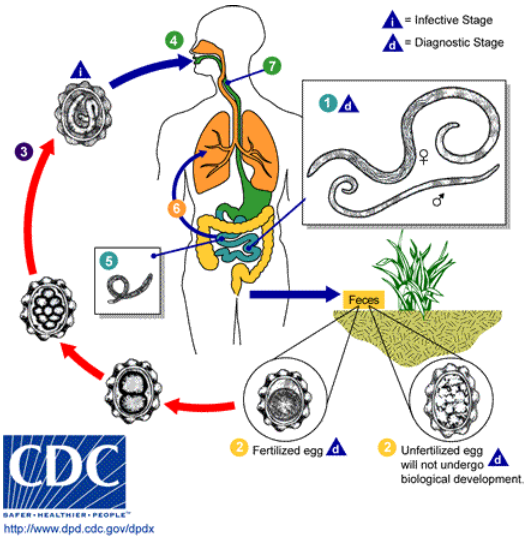

Figure: **Ascariasis Life Cycle**: An overview and summary of the life cycle leading to Ascariasis.

Enterobius

Enterobius, referred to as pinworm, is a type of parasitic nematode that is commonly found in the intestine of children. This infection is often called enterobiasis. The entire life cycle of the pinworm occurs within the human gastrointestinal tract. The life cycle begins with ingestion or insertion of eggs in the anus that have been transmitted via human-to-human contact. The life cycle of the *Enterobious* ends with eggs laid in the anus and transfered to surfaces that come in contact with this region, such as fingernails, hands, night-clothing and bed linens. Infection by pinworm is more prevalent in children due to their behaviors. Upon infection with eggs, they travel to the small intestine and hatch. The pinworm larvae will then migrate towards the colon and undergo molting which allows for further development. After two molt cycles, the larvae have developed into adults. The pinworms exhibit the ability to mate in the small intestine. Shortly after mating, the male worms die and are passed out via the feces. However, the female pinworms will attach to the mucus and wait for the egg-laying process to begin. The egg-laying process

begins with the migration of the females towards the rectum. The eggs, which are covered with a sticky covering, are then released and deposited on the outside or near the anus. The cycle begins again once eggs are ingested and infect an additional host.

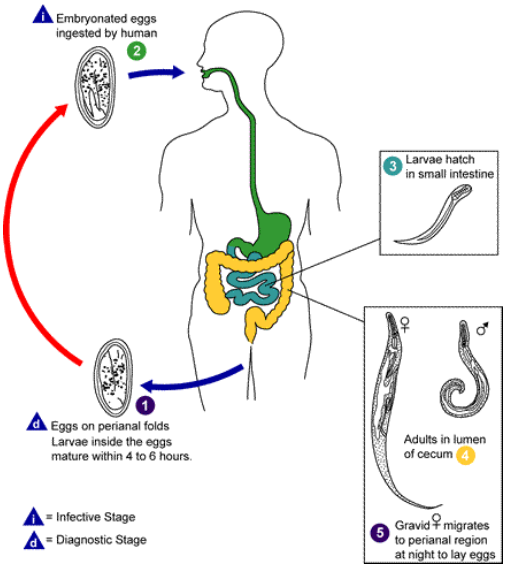

Figure: ***Overview of the pinworm life cycle****: Overview of the pinworm life cycle, specifically Enterobius vermicularis.*

Key Points

- Parasitic nematodes often contain specific body structures which promote parasitic behaviors such as ridges, rings or bristles that allow for attachment.
- Two major types of roundworms that commonly infect humans include Ascaris and Enterobious.
- Ascariasis is a disease that is caused by the parasitic roundworm Ascaris lumbricoides and is transmitted by ingesting food contaminated with Ascaris eggs.
- Enterobius, referred to as pinworm, causes enterobiasis and is commonly found in the intestine of children. The entire life cycle of the pinworm occurs within the human gastrointestinal tract.

Key Terms

- **visceral**: of or relating to the viscera – the internal organs of the body
- **nematode**: A small invertebrate animal of the phylum Nematoda.

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SECTION OVERVIEW

15.21: Microbial Diseases of the Genitourinary System

Topic hierarchy

15.21A: Overview of the Male and Female Reproductive Systems

15.21B: Overview of the Urinary System

15.21C: Normal Genitourinary Microbiota

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15.21A: Overview of the Male and Female Reproductive Systems

The human reproductive system functions to produce human offspring, with the male providing sperm and the female providing the ovum.

Learning Objectives

- Summarize the reproductive systems of men and women

Key Points

- The male reproductive system consists of external organs. The testes in the scrotum produce the male gamete, sperm, which is ejaculated in seminal fluid by the penis.
- The female reproductive system primarily consists of internal organs. The female gamete, ovum, is produced in the ovaries and is released monthly to travel to the uterus via the Fallopian tubes.
- Fertilization can occur if the penis is inserted through the vulva into the vagina and sperm is ejaculated towards the cervix. If an ovum is currently in the uterus, it can then be fertilized by sperm that manage to enter the cervix.
- Once fertilized, an ovum becomes a zygote and if all goes well, develops into a fetus in the uterus.
- Natural birth occurs when the fetus is pushed from the vagina after nine months in the uterus.

Key Terms

- **fallopian tubes**: The Fallopian tubes, also known as oviducts, uterine tubes, and salpinges (singular salpinx) are two very fine tubes lined with ciliated epithelia leading from the ovaries of female mammals into the uterus, via the utero-tubal junction.
- **penis**: The male sexual organ for copulation and urination; the tubular portion of the male genitalia (excluding the scrotum).
- **vagina**: A fibromuscular tubular tract which is the female sex organ and has two main functions: sexual intercourse and childbirth.

The reproductive system or genital system is a set of organs within an organism that work together to produce offspring. Many non-living substances, such as fluids, hormones, and pheromones, are important accessories to the reproductive system. Unlike most organ systems, the sexes of differentiated species often have significant differences. These differences allow for a combination of genetic material between two individuals and thus the possibility of greater genetic fitness of the offspring.

The Reproductive Process

Human reproduction takes place as internal fertilization by sexual intercourse. During this process, the erect penis of the male is inserted into the female's vagina until the male ejaculates semen, which contains sperm, into the vagina. The sperm travels through the vagina and cervix into the uterus for potential fertilization of an ovum. Upon successful fertilization and implantation, gestation of the fetus occurs within the female's uterus for approximately nine months (pregnancy). Gestation ends with labor resulting in birth. In labor, the uterine muscles contract, the cervix dilates, and the baby passes out through the vagina. Human babies and children are nearly helpless and require high levels of parental care for many years. One important type of parental care is the use of the mammary glands in the female breasts to nurse the baby.

The Male Reproductive System

The human male reproductive system is a series of organs located outside of the body and around the pelvic region. The primary direct function of the male reproductive system is to provide the male gamete or spermatozoa for fertilization of the ovum. The major reproductive organs of the male can be grouped into three categories. The first category is sperm production and storage. Production takes place in the testes, housed in the temperature-regulating scrotum. Immature sperm then travel to the epididymis for development and storage. The second category, the ejaculatory fluid-producing glands, includes the seminal vesicles, prostate, and vas deferens. The final category, used for copulation and deposition of the spermatozoa (sperm) within the female, includes the penis, urethra, vas deferens, and Cowper's gland.

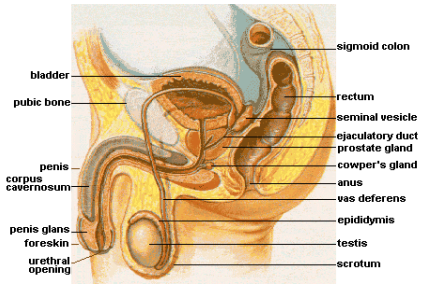

Figure: **The Human Male Reproductive System**: Cross-sectional diagram of the male reproductive organs.

Only our species has a distinctive mushroom-capped glans, which is connected to the shaft of the penis by a thin tissue of frenulum (the delicate tab of skin just beneath the urethra). One of the most significant features of the human penis is the coronal ridge underneath the gland around the circumference of the shaft. Magnetic imaging studies of heterosexual couples having sex reveal that during coitus, the typical penis expands to fill the vaginal tract, and with full penetration can even reach the woman's cervix and lift her uterus. This combined with the fact that human ejaculate is expelled with great force and considerable distance (up to two feet if not contained), suggests that men are designed to release sperm into the uppermost portion of the vagina. This may be an evolutionary adaptation to expel the semen left by other males while at the same time increasing the possibility of fertilization with the current male's semen.

The Female Reproductive System

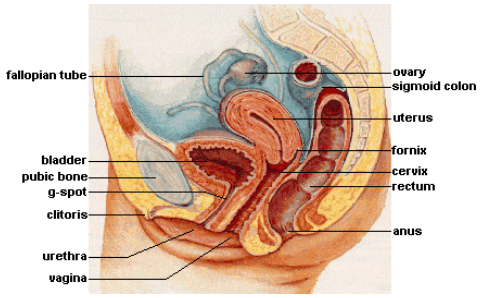

Figure: **The Human Female Reproductive System**: The female reproductive system is largely internal.

The human female reproductive system is a series of organs primarily located inside the body and around the pelvic region. It contains three main parts: the vagina, which leads from the vulva, the vaginal opening, to the uterus; the uterus, which holds the developing fetus; and the ovaries, which produce the female's ova. The breasts are also a reproductive organ during parenting, but are usually not classified as part of the female reproductive system. The vagina meets the outside at the vulva, which also includes the labia, clitoris, and urethra. During intercourse, this area is lubricated by mucus secreted by the Bartholin's glands. The vagina is attached to the uterus through the cervix, while the uterus is attached to the ovaries via the Fallopian tubes. At certain intervals, approximately every 28 days, the ovaries release an ovum that passes through the Fallopian tube into the uterus.

If the ova is fertilized by sperm, it attaches to the endometrium and the fetus develops. In months when fertilization does not occur, the lining of the uterus, called the endometrium, and unfertilized ova are shed each cycle through a process known as menstruation.

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15.21B: Overview of the Urinary System

Learning Objectives

- Review the urinary system

The Renal System

The renal system, which is also called the urinary system, is a group of organs in the body that filters out excess fluid and other substances from the bloodstream. The purpose of the renal system is to eliminate wastes from the body, regulate blood volume and pressure, control levels of electrolytes and metabolites, and regulate blood pH.

The renal system organs include the kidneys, ureters, bladder, and urethra. Metabolic wastes and excess ions are filtered out of the blood, along with water, and leave the body in the form of urine.

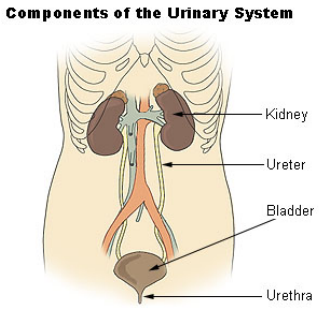

Figure: **Components of the renal system**: Here are the major organs of the renal system.

Renal System Functions

The renal system has many functions. Many of these functions are interrelated with the physiological mechanisms in the cardiovascular and respiratory systems.

1. Removal of metabolic waste products from the body (mainly urea and uric acid).
2. Regulation of electrolyte balance (e.g., sodium, potassium, and calcium).
3. Osmoregulation controls the blood volume and body water contents.
4. Blood pressure homeostasis: The renal system alters water retention and thirst to slowly change blood volume and keep blood pressure in a normal range.
5. Regulation of acid-base homeostasis and blood pH, a function shared with the respiratory system.

Many of these functions are related to one another as well. For example, water follows ions via an osmotic gradient, so mechanisms that alter sodium levels or sodium retention in the renal system will alter water retention levels as well.

Organs of the Renal System

Kidneys and Nephrons

Kidneys are the most complex and critical part of the urinary system. The primary function of the kidneys is to maintain a stable internal environment (homeostasis) for optimal cell and tissue metabolism. The kidneys have an extensive blood supply from the renal arteries that leave the kidneys via the renal vein.

Nephrons are the main functional component inside the parenchyma of the kidneys, which filter blood to remove urea, a waste product formed by the oxidation of proteins, as well as ions like potassium and sodium. The nephrons are made up of a capsule capillaries (the glomerulus) and a small renal tube. The renal tube of the nephron consists of a network of tubules and loops that are selectively permeable to water and ions. Many hormones involved in homeostasis will alter the permeability of these tubules to change the amount of water that is retained by the body.

Ureter

Urine passes from the renal tube through tubes called ureters and into the bladder.

Bladder

The bladder is flexible and is used as storage until the urine is allowed to pass through the urethra and out of the body.

Urethra

The female and male renal system are very similar, differing only in the length of the urethra.

Human Osmoregulation

The kidneys play a very large role in human osmoregulation by regulating the amount of water reabsorbed from the glomerular filtrate in kidney tubules, which is controlled by hormones such as antidiuretic hormone (ADH), renin, aldosterone, and angiotensin I and II.

A basic example is that a decrease in water concentration of blood is detected by osmoreceptors in the hypothalamus, which stimulates ADH release from the pituitary gland to increase the permeability of the wall of the collecting ducts and tubules in the nephrons. Therefore, a large proportion of water is reabsorbed from fluid to prevent a fair proportion of water from being excreted.

The extent of blood volume and blood pressure regulation facilitated by the kidneys is a complex process. Besides ADH secretion, the renin-angiotensin feedback system is critically important to maintain blood volume and blood pressure homeostasis.

Key Points

- The renal system eliminate wastes from the body, controls levels of electrolytes and metabolites, controls the osmoregulation of blood volume and pressure, and regulates blood pH.
- The renal system organs include the kidneys, ureter, bladder, and urethra. Nephrons are the main functional component of the kidneys.
- The respiratory and cardiovascular systems have certain functions that overlap with renal system functions.
- Metabolic wastes and excess ions are filtered out of the blood, combined with water, and leave the body in the form of urine.
- A complex network of hormones controls the renal system to maintain homeostasis.

Key Terms

- **ureter**: These are two long, narrow ducts that carry urine from the kidneys to the urinary bladder.
- **osmoregulation**: The most important function of the renal system, in which blood volume, blood pressure, and blood osmolarity (ion concentration) is maintained in homeostasis.

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15.21C: Normal Genitourinary Microbiota

The vaginal microflora consist mostly of various lactobacillus species.

Learning Objectives

- Recognize the types of bacteria present in the vaginal microflora

Key Points

- If microbe numbers grow beyond their typical ranges (often due to a compromised immune system) or if microbes populate atypical areas of the body (such as through poor hygiene or injury), disease can result.
- Disturbance of the vaginal flora can lead to bacterial vaginosis.

Key Terms

- **urinary tract infection**: Finding bacteria or other microorganisms, such as yeasts, in bladder urine with or without clinical symptoms and with or without renal disease.

The Genitourinary Microbiome

The human microbiome, or human microbiota, is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect. Those that are expected to be present and that under normal circumstances do not cause disease, but instead participate in maintaining health, are deemed members of the normal flora.

Populations of microbes inhabit the skin and mucosa. Their role forms part of normal, healthy human physiology; however, if microbe numbers grow beyond their typical ranges (often due to a compromised immune system) or if microbes populate atypical areas of the body (such as through poor hygiene or injury), disease can result.

Proportions of Microbes

It is estimated that 500 to 1000 species of bacteria live in the human gut and a roughly similar number on the skin. Bacterial cells are much smaller than human cells, and there are at least ten times as many bacteria as human cells in the body (approximately 10^{14} versus 10^{13}). Normal flora bacteria can act as opportunistic pathogens at times of lowered immunity.The vaginal microflora consist mostly of various lactobacillus species. It was long thought that the most common of these species was Lactobacillus acidophilus, but it has later been shown that the most common one is L. iners followed by L. crispatus. Other lactobacilli found in the vagina are L. jensenii, L. delbruekii and L. gasseri. Disturbance of the vaginal flora can lead to bacterial vaginosis.

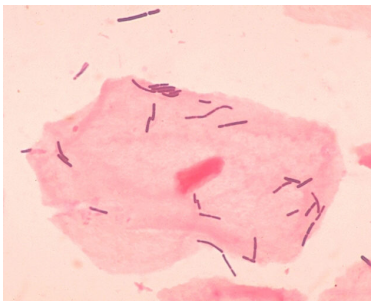

Figure: **Lactobacillus**: Lactobacilli and a vaginal squamous cell.

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SECTION OVERVIEW

15.22: Bacterial Diseases of the Urinary System

Topic hierarchy

15.22A: Urinary Tract Infection (UTI)

15.22B: Cystitis

15.22C: Pyelonephritis

15.22D: Leptospirosis

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15.22A: Urinary Tract Infection (UTI)

A urinary tract infection (UTI) is an infection affecting the urinary tract; about 150 million people develop UTIs each year.

LEARNING OBJECTIVES

Summarize the various categories of urinary tract infection (UTI): complicated, uncomplicated, upper and lower UTIs

KEY TAKEAWAYS

Key Points

- About 150 million people develop a urinary tract infection each year, and they are more common in women than men.
- A urinary tract infection (UTI) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a bladder infection (cystitis); when it affects the upper urinary tract it is known as kidney infection (pyelonephritis).
- UTIs are generally treatable with antibiotics, though resistance to some of the medications is growing.

Key Terms

- **urinary tract infection**: A bacterial infection that affects part of the urinary tract.

About 150 million people develop a urinary tract infection each year. They are more common in women than men. In women, they are the most common form of bacterial infection. Up to 10% of women have a urinary tract infection in a given year and half of women having at least one infection at some point in their lives. They occur most frequently between the ages of 16 and 35 years. Recurrences are common. Urinary tract infections have been described since ancient times with the first documented description in the Ebers Papyrus dated to c. 1550 BC.

A urinary tract infection (UTI) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a bladder infection (cystitis); when it affects the upper urinary tract it is known as kidney infection (pyelonephritis). Symptoms from a lower urinary tract include pain with urination, frequent urination, and feeling the need to urinate despite having an empty bladder. Symptoms of a kidney infection include fever and flank pain usually in addition to the symptoms of a lower UTI. Rarely the urine may appear bloody. In the very old and the very young, symptoms may be vague or non-specific.

The most common cause of infection is Escherichia coli, though other bacteria or fungi may rarely be the cause. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history. Although sexual intercourse is a risk factor, UTIs are not classified as sexually transmitted infections (STIs). Kidney infection, if it occurs, usually follows a bladder infection but may also result from a blood-borne infection. Diagnosis in young healthy women can be based on symptoms alone. In those with vague symptoms, diagnosis can be difficult because bacteria may be present without there being an infection. In complicated cases or if treatment fails, a urine culture may be useful.

Categories of UTI

Uncomplicated UTIs

In uncomplicated cases, a diagnosis may be made and treatment given based on symptoms alone without further laboratory confirmation, and treatment involves a short course of antibiotics such as nitrofurantoin or trimethoprim / sulfamethoxazole. Resistance to many of the antibiotics used to treat this condition is increasing.

Complicated UTIs

In complicated cases, it may be useful to confirm the diagnosis via urinalysis, looking for the presence of urinary nitrites, white blood cells (leukocytes), or leukocyte esterase. Another test, urine microscopy, looks for the presence of red blood cells, white blood cells, or bacteria. A longer course or intravenous antibiotics may be needed. If symptoms do not improved in two or three days, further diagnostic testing may be needed. Phenazopyridine may help with symptoms. In those who have bacteria or white blood cells in their urine but have no symptoms, antibiotics are generally not needed, although during pregnancy is an exception. In those with frequent infections, a short course of antibiotics may be taken as soon as symptoms begin or long term antibiotics may be used as a preventative measure.

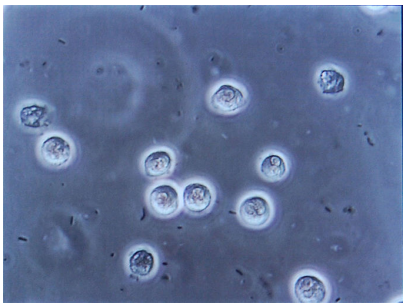

Figure: **Bacteriuria and Pyuria**: Multiple bacilli (rod-shaped bacteria, here shown as black and bean-shaped) shown between white blood cells in urinary microscopy. These changes are indicative of a urinary tract infection.

Lower UTI

Lower urinary tract infection is also referred to as a bladder infection. The most common symptoms are burning with urination and having to urinate frequently (or an urge to urinate) in the absence of vaginal discharge and significant pain. These symptoms may vary from mild to severe and in healthy women last an average of six days. Some pain above the pubic bone or in the lower back may be present.

Upper UTI

People experiencing an upper urinary tract infection, or pyelonephritis, may experience flank pain, fever, or nausea and vomiting in addition to the classic symptoms of a lower urinary tract infection. Rarely the urine may appear bloody or contain visible pus in the urine.

Prevention

A number of measures have not been confirmed to affect UTI frequency including: urinating immediately after intercourse, the type of underwear used, personal hygiene methods used after urinating or defecating, or whether a person typically bathes or showers. There is similarly a lack of evidence surrounding the effect of holding one's urine, tampon use, and douching. In those with frequent urinary tract infections who use spermicide or a diaphragm as a method of contraception, they are advised to use alternative methods. In those with benign prostatic hyperplasia urinating in a sitting position appears to improve bladder emptying which might decrease urinary tract infections in this group.

For those with recurrent infections, taking a short course of antibiotics when each infection occurs is associated with the lowest antibiotic use. A prolonged course of daily antibiotics is also effective. Medications frequently used include nitrofurantoin and trimethoprim/sulfamethoxazole (TMP/SMX). Methenamine is another agent used for this purpose as in the bladder where the acidity is low it produces formaldehyde to which resistance does not develop. Some recommend against prolonged use due to concerns of antibiotic resistance.

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15.22B: Cystitis

Learning Objectives

- Differentiate among the distinct types of cystitis: traumatic, interstitial, eosinophilic, hemorrhagic cystitis, and cystitis cystica, recognizing their causes and risk factors

A urinary tract infection (UTI), a bacterial infection that affects the lower urinary tract, is also known as a simple cystitis (a bladder infection). Symptoms from a lower urinary tract infection include painful urination and either frequent urination or the urge to urinate (or both). Cystitis is a urinary bladder inflammation that can result from any one of a number of distinct syndromes. It is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection.



Figure: ***Proteus vulgaris on MacConkey agar****: After 24 hours, this inoculated MacConkey agar culture plate cultivated colonial growth of Gram-negative, rod-shaped, and facultatively anaerobic Proteus vulgaris bacteria. Normally found in the humans gastrointestinal tract, Proteus spp. are opportunistic pathogens, which means that they usually do not cause disease. However, under immunocompromised circumstances, i.e., weakened immunity, these bacteria can be found the culprit responsible for urinary tract infections such as cystitis and pyelonephritis.*

Signs and Symptoms

- Pressure in the lower pelvis
- Painful urination (dysuria)
- Frequent urination (polyuria) or urgent need to urinate (urinary urgency)
- Need to urinate at night (nocturia)
- Urine that contains traces of blood (haematuria)
- Dark, cloudy or strong-smelling urine
- Pain above the pubic bone, or in the lower back or abdomen
- Feeling unwell, weak, or feverish

There are several medically distinct types of cystitis, each having a unique etiology and therapeutic approach:

- Traumatic cystitis is probably the most common form of cystitis in the female. It is due to bruising of the bladder, usually by abnormally forceful sexual intercourse. This is often followed by bacterial cystitis, frequently by coliform bacteria being transferred from the bowel through the urethra into the bladder.
- Interstitial cystitis (IC) is considered more of an injury to the bladder resulting in constant irritation and rarely involves the presence of infection. IC patients are often misdiagnosed with UTI/cystitis for years before they are told that their urine cultures are negative. Antibiotics are not used to treatment of IC. The cause of IC is unknown, although some suspect it may be autoimmune where the immune system attacks the bladder. Several therapies are now available.
- Eosinophilic cystitis (EC) is a rare form of cystitis that is diagnosed via biopsy. In these cases, the bladder wall is infiltrated with a high number of eosinophils. The cause of EC may be attributed to infection by Schistosoma haematobium or by certain medications in afflicted children. Some consider it a form of interstitial cystitis.
- Hemorrhagic cystitis can occur as a side effect of cyclophosphamide, ifosfamide, and radiation therapy. Radiation cystitis, one form of hemorrhagic cystitis is a rare consequence of patients undergoing radiation therapy for the treatment of cancer. Several adenovirus serotypes have been associated with an acute, self-limited hemorrhagic cystitis, which occurs primarily in boys. It is

characterized by hematuria, and virus can usually be recovered from the urine. In sexually active women the most common cause of urinary tract infection is from E. coli and Staphylococcus saprophyticus.

- Cystitis cystica is a chronic cystitis glandularis accompanied by the formation of cysts. This disease can cause chronic urinary tract infections. It appears as small cysts filled with fluid and lined by one or more layers of epithelial cells. These are due to hydropic degeneration in center of Brunn's nests

Key Points

- Cystitis is a urinary bladder inflammation that is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection. Symptoms from a lower urinary tract include painful urination and either frequent urination or urge to urinate (or both), but neither may be present.
- Traumatic cystitis is probably the most common form of cystitis in the female. It is due to bruising of the bladder, usually by abnormally forceful sexual intercourse.
- Interstitial cystitis (IC) is considered more of an injury to the bladder resulting in constant irritation and rarely involves the presence of infection.

Key Terms

- **cystitis**: Cystitis is a urinary bladder inflammation that can result from any one of a number of distinct syndromes. It is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection.

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15.22C: Pyelonephritis

Learning Objectives

- Identify the main symptoms of pyelonephritis

Pyelonephritis is an inflammation of the kidney tissue, calyces, and renal pelvis. It is commonly caused by bacterial infection that has spread up the urinary tract or travelled through the bloodstream to the kidneys. A similar term is “pyelitis” which means inflammation of the pelvis and calyces. In other words, pyelitis together with nephritis is collectively known as pyelonephritis. Severe cases of pyelonephritis can lead to pyonephrosis (pus accumulation around the kidney), sepsis (a systemic inflammatory response of the body to infection), kidney failure and even death.

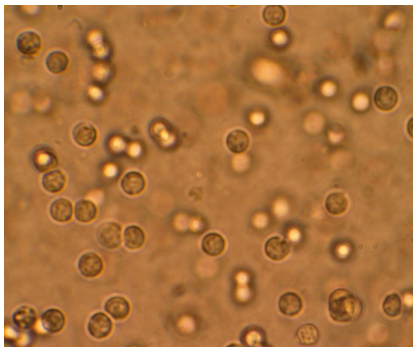

Figure: ***Urinary tract infection (UTI)****: White blood cells in the urine of someone with a UTI, seen under a microscope.*

Pyelonephritis presents with fever, accelerated heart rate, painful urination, abdominal pain radiating to the back, nausea, and tenderness at the costovertebral angle on the affected side. Pyelonephritis that has progressed to urosepsis may be accompanied by signs of septic shock, including rapid breathing, decreased blood pressure, violent shivering, and occasionally delirium. Pyelonephritis requires antibiotic therapy, and sometimes surgical intervention, as well as treatment of any underlying causes to prevent its recurrence.

Key Points

- Pyelonephritis is an inflammation of the kidney tissue and renal area of the pelvis.
- Pyelonephritis is most commonly caused by a bacterial infection ascending up the upper urinary tract.
- Severe cases of pyelonephritis can lead to sepsis, kidney failure, and death.
- Pyelonephritis presents with fever, accelerated heart rate, painful urination, abdominal pain, and nausea.
- Pyelonephritis requires antibiotic therapy, and sometimes surgical intervention, as well as treatment of any underlying causes to prevent recurrence.

Key Terms

- **pyelonephritis**: An ascending urinary tract infection that has reached the pelvis or the kidney.
- **Urinary tract**: The organ system that produces, stores, and eliminates urine. In humans it includes two kidneys, two ureters, the bladder, and the urethra.

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15.22D: Leptospirosis

Learning Objectives

- Generalize the causes and mode of transmission for leptospirosis

Leptospirosis (also known as Weil's Syndrome, canicola fever, canefield fever, nanukayami fever, 7-day fever, Rat Catcher's Yellows, Fort Bragg fever, black jaundice, and Pretibial fever) is caused by bacteria of the genus *Leptospira*, and affects humans as well as other animals. Symptoms can range from none to mild such as headaches, muscle pains, and fevers; to severe with bleeding from the lungs or meningitis. If the infection causes the person to turn yellow, have kidney failure and bleeding it is then known as Weil's disease. If the infection causes lots of bleeding from the lungs it is known as severe pulmonary haemorrhage syndrome.

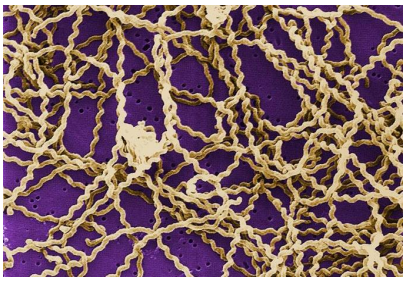

Figure: ***Leptospira bactera that cause Leptospirosis****: Scanning electron micrograph of a number of Leptospira sp. bacteria atop a 0.1 µm polycarbonate filter.*

Leptospirosis is among the world's most common diseases transmitted to people from animals. The infection is commonly transmitted to humans by allowing water that has been contaminated by animal urine to come in contact with unhealed breaks in the skin, eyes, or mucous membranes. Outside of tropical areas, leptospirosis cases have a relatively distinct seasonality, with most cases occurring in spring and autumn.

Leptospirosis is caused by a spirochaete bacterium called *Leptospira spp*. There are at least five serotypes of importance in the United States and Canada, all of which cause disease in dogs (Icterohaemorrhagiae, Canicola, Pomona, Grippotyphosa, and Bratislava).There are other (less common) infectious strains as well. Leptospirosis is transmitted by the urine of an infected animal and is contagious as long as it is still moist. Although rats, mice, and moles are important primary hosts, a wide range of other mammals (including dogs, deer, rabbits, hedgehogs, cows, sheep, raccoons, opossums, skunks, and certain marine mammals) are able to carry and transmit the disease as secondary hosts. Dogs may lick the urine of an infected animal off the grass or soil or drink from an infected puddle.

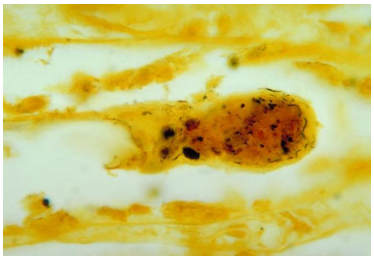

Figure: ***Leptospirosis in kidney****: Photomicrograph of kidney tissue, using a silver staining technique, revealing the presence of Leptospira bacteria.*

There have been reports of "house dogs" contracting leptospirosis from licking the urine of infected mice that enter the house. The type of habitats most likely to carry infectious bacteria are muddy riverbanks, ditches, gullies, and muddy livestock-rearing areas where there is regular passage of either wild or farm mammals. There is a direct correlation between the amount of rainfall and the incidence of leptospirosis, making it seasonal in temperate climates and year-round in tropical climates. Leptospirosis is also transmitted by the semen of infected animals. Humans become infected through contact with water, food, or soil containing urine from these infected animals. This may result from swallowing contaminated food and water or through skin contact. The disease is not known to be spread from person to person, and cases of bacterial dissemination in convalescence are extremely rare in humans. Leptospirosis is common among water-sport enthusiasts in specific areas, as prolonged immersion in water is known to promote the entry of the bacteria. Surfers and whitewater paddlers are at especially high risk in areas that have been shown to contain the

bacteria, and can contract the disease by swallowing contaminated water, splashing contaminated water into their eyes or nose, or exposing open wounds to infected water.

Key Points

- Leptospirosis symptoms can range from none to mild such as headaches, muscle pains, and fevers; to severe with bleeding from the lungs or meningitis.
- Outside of tropical areas, leptospirosis cases have a relatively distinct seasonality, with most cases occurring in spring and autumn.
- Leptospirosis is transmitted by the urine of an infected animal and is contagious as long as it remains moist.
- There is a direct correlation between the amount of rainfall and the incidence of leptospirosis, making it seasonal in temperate climates and year-round in tropical climates.

Key Terms

- **leptospirosis**: an acute, infectious, febrile disease of both humans and animals, caused by spirochetes of the genus Leptospira

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- Scanning electron micrographu00a0of a number of Leptospira sp. bacteria atop a 0.1 u00b5mu00a0polycarbonateu00a0filter. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/Leptosp...micrograph.jpg**. **License**: ***Public Domain: No Known Copyright***

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SECTION OVERVIEW

15.23: Bacterial Diseases of the Reproductive System

Topic hierarchy

15.23A: Prostatitis

15.23B: Prostatitis

15.23C: Gonorrhea

15.23D: Nongonococcal Urethritis (NGU)

15.23E: Pelvic Inflammatory Disease (PID)

15.23F: Syphilis

15.23G: Genital Ulcer Diseases

15.23H: Lymphogranuloma Venereum

15.23I: Group B Streptococcus Colonization

15.23J: Chancroid (Soft Chancre)

15.23K: Bacterial Vaginosis

15.23L: Chlamydia

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15.23A: Prostatitis

Prostatitis is an inflammation of the prostate which can be caused by bacteria.

Learning Objectives

- Define the symptoms, diagnostic tests and treatments used for prostatitis

Key Points

- Bacteria can cause acute and chronic prostatitis.
- Acute prostatitis is a serious condition that needs immediate treatment with antibiotics. If treated promptly complications are rare.
- Chronic prostatitis is a rare disease that is harder to treat and has high recurrence rate. In the case of remission, combinations of antibiotics may be a better therapy than a single antibiotic.

Key Terms

- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.
- **cystitis**: An inflammation of the urinary bladder.

Prostatitis is an inflammation of the prostate which can be caused by bacteria. Bacterial infections can cause both acute and chronic prostatitis.

Symptoms and diagnosis

Acute prostatitis is relatively easy to diagnose because it presents the general infection symptoms which may include: fever, chills, groin and lower back pain, issues during urination, and general body aches. The prostate is usually enlarged. Testing of urine samples reveals the presence of bacteria and white blood cells. Blood samples can contain bacteria. White blood cells counts are elevated in the complete blood count.

Chronic prostatitis is a rare condition. It usually causes intermittent urinary tract infections (UTIs) which can lead to cystitis. Sometimes there are no symptoms. The diagnosis is made after culturing urine or prostate liquid. Semen analysis can also be used for diagnosis it. PSA (prostate specific antigen) levels may be elevated.

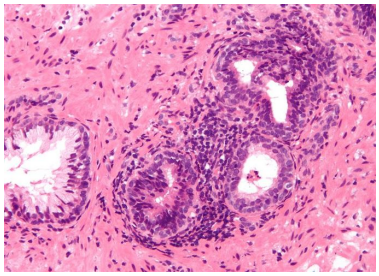

Figure: **Histologic image of chronic prostatitis**: The single gland on the left is healthy, while the glands on the right are inflamed

INFECTIOUS AGENTS

Common bacteria that cause acute prostatitis include gram negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, as well as gram positive bacteria such as *Staphylococcus aureus*. E. coli is the major infectious agent that causes chronic prostatitis.

TREATMENT

Acute prostatitis is a serious condition that requires immediate treatment to prevent complications such as sepsis. The antibiotics of choice should be bactericidal (e.g., quinolone) not bacteriostatic (e.g., tetracycline) if the infection is life-threatening. Other commonly used antibiotics are doxycycline and ciprofloxacin. Severe infections may require hospitalization, while milder cases (no sepsis) can be treated with antibiotic administration combined with bed rest at home. The infection is usually cured successfully

with antibiotics and the recovery is complete without further complications. Treatment of chronic prostatitis requires courses of antibiotic administration for one to two months or a longer course with low doses. The recurrence of the disease is high. In these cases higher success rates of treatment are achieved when a combination of antibiotics is used. Animal studies have shown that *E. coli* extract with cranberry can prevent chronic prostatitis. The choice of antibiotic for chronic prostatitis also depends on its ability to penetrate the prostatic capsule. Good penetrators of the barrier are quinolones, doxycycline, macrolides and sulfas (Bactrim). In the case of acute prostatitis, the prostate-blood barrier is damaged by the infection so the penetrating ability of the antibiotic is not as important.

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15.23B: Prostatitis

Prostatitis is an inflammation of the prostate which can be caused by bacteria.

Learning Objectives

- Define the symptoms, diagnostic tests and treatments used for prostatitis

Key Points

- Bacteria can cause acute and chronic prostatitis.
- Acute prostatitis is a serious condition that needs immediate treatment with antibiotics. If treated promptly complications are rare.
- Chronic prostatitis is a rare disease that is harder to treat and has high recurrence rate. In the case of remission, combinations of antibiotics may be a better therapy than a single antibiotic.

Key Terms

- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.
- **cystitis**: An inflammation of the urinary bladder.

Prostatitis is an inflammation of the prostate which can be caused by bacteria. Bacterial infections can cause both acute and chronic prostatitis.

Symptoms and diagnosis

Acute prostatitis is relatively easy to diagnose because it presents the general infection symptoms which may include: fever, chills, groin and lower back pain, issues during urination, and general body aches. The prostate is usually enlarged. Testing of urine samples reveals the presence of bacteria and white blood cells. Blood samples can contain bacteria. White blood cells counts are elevated in the complete blood count.

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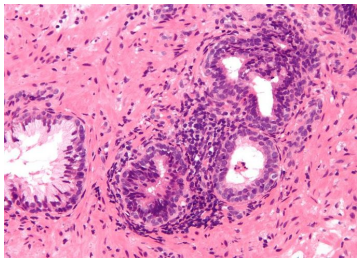

Figure: **Histologic image of chronic prostatitis**: The single gland on the left is healthy, while the glands on the right are inflamed

INFECTIOUS AGENTS

Common bacteria that cause acute prostatitis include gram negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, as well as gram positive bacteria such as *Staphylococcus aureus*. E. coli is the major infectious agent that causes chronic prostatitis.

TREATMENT

Acute prostatitis is a serious condition that requires immediate treatment to prevent complications such as sepsis. The antibiotics of choice should be bactericidal (e.g., quinolone) not bacteriostatic (e.g., tetracycline) if the infection is life-threatening. Other commonly used antibiotics are doxycycline and ciprofloxacin. Severe infections may require hospitalization, while milder cases (no sepsis) can be treated with antibiotic administration combined with bed rest at home. The infection is usually cured successfully with antibiotics and the recovery is complete without further complications. Treatment of chronic prostatitis requires courses of

antibiotic administration for one to two months or a longer course with low doses. The recurrence of the disease is high. In these cases higher success rates of treatment are achieved when a combination of antibiotics is used. Animal studies have shown that *E. coli* extract with cranberry can prevent chronic prostatitis. The choice of antibiotic for chronic prostatitis also depends on its ability to penetrate the prostatic capsule. Good penetrators of the barrier are quinolones, doxycycline, macrolides and sulfas (Bactrim). In the case of acute prostatitis, the prostate-blood barrier is damaged by the infection so the penetrating ability of the antibiotic is not as important.

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15.23C: Gonorrhea

Gonorrhea (also colloquially known as the clap) is a common human sexually transmitted infection caused by the bacterium Neisseria gonorrhoeae.

Learning Objectives

- Describe gonorrhea

Key Points

- The usual symptoms of gonorrhea in men are burning with urination and penile discharge.
- Women with gonorrhea, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain.
- If gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.Treatment is commonly with ceftriaxone as antibiotic resistance has developed to many previously used medications.

Key Terms

- **ceftriaxone**: A synthetic cephalosporin antibiotic used to treat gonorrhea.

Gonorrhea (also colloquially known as the clap) is a common human sexually transmitted infection. The usual symptoms in men are burning with urination and penile discharge. Women, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain. In both men and women if gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.Treatment is commonly with ceftriaxone as antibiotic resistance has developed to many previously used medications. In 2011, there were reports of some strains of gonorrhea showing resistance to ceftriaxone. Half of women with gonorrhea are asymptomatic while others have vaginal discharge, lower abdominal pain or pain with intercourse.

The most common male symptoms are urethritis associated with burning with urination and discharge from the penis. Either sex may also acquire gonorrhea of the throat from performing oral sex on an infected partner, usually a male partner. Such infection is asymptomatic in 90% of cases, and produces a sore throat in the remaining 10%. The incubation period is 2 to 14 days with most of these symptoms occurring between 4–6 days after being infected. Rarely, gonorrhea may cause skin lesions and joint infection (pain and swelling in the joints) after traveling through the blood stream. Very rarely it may settle in the heart causing endocarditis or in the spinal column causing meningitis (both are more likely among individuals with suppressed immune systems, however).

CAUSE

Gonorrhea is caused by the bacteria Neisseria gonorrhoeae. The infection is transmitted from one person to another through vaginal, oral, or anal sex. Men have a 20% risk of getting the infection from a single act of vaginal intercourse with an infected woman. The risk for men who have sex with men is higher. Women have a 60–80% risk of getting the infection from a single act of vaginal intercourse with an infected man. A mother may transmit gonorrhea to her newborn during childbirth; when affecting the infant's eyes, it is referred to as ophthalmia neonatorum. It cannot be spread by toilets or bathrooms.

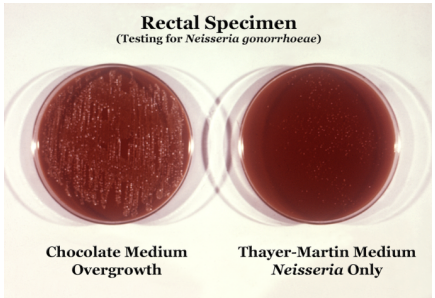

Figure: **Neisseria gonorrhoeae**: Neisseria gonorrhoeae cultured on two different media types and presented in stereoscopic 3d.

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15.23D: Nongonococcal Urethritis (NGU)

Nongonococcal urethritis (NGU) is an urethral inflammation that is not caused by *Neisseria gonorrhoeae*.

Learning Objectives

- Recognize the symptoms, causes and treatments for nongonococcal urethritis (NGU)

Key Points

- The general symptoms are pain on urination, frequent urination, and white or cloudy discharge.
- It can be caused by many infectious agents, with the most common being chlamydia.
- Since many different infectious agents can be causing NGU, the initial treatment should be with a broad spectrum antibiotic.

Key Terms

- **epididymitis**: An inflammation of the epididymis, a structure in the testicles where sperm matures.

Nongonococcal urethritis (NGU) is a urethral inflammation that is not caused by *Neisseria gonorrhoeae*, *a* classification used by doctors for treatment purposes. The general symptoms are pain on urination, frequent need to urinate and white or cloudy discharge. The most common symptoms unique to men are discharge from the penis, itching, and tenderness. In women, the symptoms include vaginal discharge, abdominal pain. If irregular menstrual bleeding is present it may indicate that the infection has progressed into pelvic inflammatory disease.

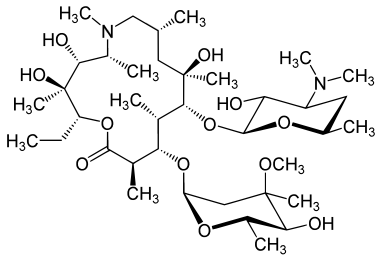

Figure: **Azithromycin**: The structure of azithromycin, a microlide antibiotic used to treat NGU.

Diagnosing NGU is based on the lack of *Neisseria gonorrhoeae* in laboratory testsin a patient with urethritis. In men, it can be diagnosed with Gram staining of urethral discharge; the same is not true for women, since they may have other Gram negative bacteria that are part of their normal vaginal microflora. There are multiple infectious agents that can cause nongonococcal inflammation of the urethra. The most common bacterial agent is *Chlamydia trachomatis* (about a quarter to half of all NGU cases), though others include *Ureaplasma urealyticum*, *Haemophilus vaginalis* and *Mycoplasma genitalium*. Viral infections can be caused sometimes by the Herpes simplex virus or adenovirus. Parasites such as *Trichomonas vaginalis* can cause inflammation too, although rarely. NGU can be caused by reasons different than infection, such as the use of some chemicals or physical injuries. Since many different infectious agents can be causing NGU, the initial treatment should be with a broad spectrum antibiotic. Studies indicate that therapies with doxycycline or azithromycin with tinidazole can be more effective than doxycycline or azithromycin alone. Sexual partners of infected patients should be treated as well. Prompt treatment is critical in both men and women. Women are at risk of developing pelvic inflammatory disease (PID), while in men the infection can progress to epididymitis and cause infertility.

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15.23E: Pelvic Inflammatory Disease (PID)

Pelvic inflammatory disease (PID) is an inflammation of the female reproductive organs that is most often caused by infection.

Learning Objectives

- Describe the causes, symptoms and long-term effects of pelvic inflammatory disease

Key Points

- Different agents can cause the infection but the most common are Chlamydia trachomatis and Neisseria gonorrhoeae.
- PID can cause permanent damage to the affected organs leading to issues such as infertility and chronic pelvic pain.
- Single antibiotics or combinations of antibiotics are used for the treatment of PID.

Key Terms

- **ectopic**: Being out of place, such as a pregnancy occurring inside the fallopian tubes instead of the uterus.
- **pelvic inflammatory disease**: inflammation of the uterus, fallopian tubes, and/or ovaries as it progresses to scar formation with adhesions to nearby tissues and organs
- **asymptomatic**: not exhibiting any symptoms of disease.

Pelvic inflammatory disease (PID) is an inflammation of the uterus, fallopian tubes and/or the ovaries. It is most often caused by a sexually transmitted infection (STI) but there are other predisposing conditions (e.g., postpartum period, the use of intrauterine device). It should be treated promptly to avoid serious complications like scarring and adhesions which can cause infertility, ectopic pregnancy and chronic pelvic pain.

Symptoms and diagnosis

PID can be asymptomatic or present with acute symptoms. About two thirds of patients whose laparoscopies indicated a previous PID were unaware of it. Asymptomatic infections should be treated as well, since they can still cause permanent damage to the reproductive tract.

Symptoms include fever, lower abdominal pain, unusual discharge, irregular menstrual bleeding, painful intercourse.

Different tests can be used for diagnosis such as pelvic ultrasound and laboratory tests for STIs. Usually, more than one test is needed for proper diagnosis. Early diagnosis and treatment are critical to limit the spread of the infection to the lower part of the tract and to avoid long term consequences.

Infectious agents

PID can be caused by many different infectious agents like viruses, fungi or bacteria. The most common infectious agents are *Chlamydia trachomatis* and *Neisseria gonorrhoeae* which are sexually transmitted.

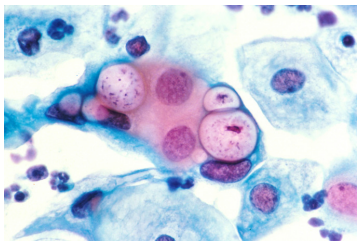

Figure: **Pap smear with Chlamydia**: Cells of Chlamydia are visible in the vacuoles. Magnification 500x, stained with hematoxylin and eosin stain (HE)

The normal vaginal flora can also cause PID under certain circumstances. Co-infection with multiple species is also possible.

Treatment

The primary mode of therapy is an antibiotic regimen. In serious cases, intravenous administration of drugs may be necessary. Usually, improvement of symptoms should be noticed within a few days.

Sexual partners of patients with PID should be treated as well. Some of the most commonly used antibiotics and combinations of antibiotics are: *cefoxitin* or *cefotetan* plus *doxycycline*, *cefoxitin* plus *doxycycline*, *clindamycin* plus *gentamycin*, *ampicillin* and *sublactam* plus *doxycycline.*

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15.23F: Syphilis

Learning Objectives

- Describe syphilis, its affect on the spinal cord, and its methods of transmission

Syphilis is a sexually transmitted infection (STI) caused by the spirochete bacterium *Treponema pallidum*.

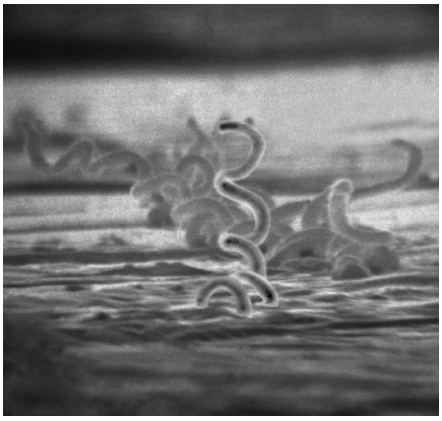

Figure: **Electron Microscopy of Treponema Pallidum**: This electron micrograph shows Treponema pallidum on cultures of cotton-tail rabbit epithelium cells (Sf1Ep). It is the causative agent of syphilis.

FOUR STAGES OF SYPHILIS

The signs and symptoms of syphilis vary depending on which of the four stages it presents (primary, secondary, latent, or tertiary). The primary stage classically presents itself with a single chancre (a firm, painless, non-itchy skin ulceration) as shown in. Secondary syphilis shows itself with a diffuse rash that frequently involves the palms of the hands and soles of the feet. Latent syphilis displays little to no symptoms, and neurosyphilis (tertiary) can result in neurological and cardiac symptoms because the syphilis has been undiagnosed or untreated for many years.



Figure: **Secondary Syphilitic Infection on the Posterior Aspect of the Torso**: Dermatologic manifestations are the hallmark of secondary syphilis. Copper-red papules are most common, but macular, pustular, acneiform, psoriasiform, nodular, annular, or follicular variants can appear. The lesions characteristically do not itch, but may itch in some patients.



Figure: **Primary Syphilitic Infection of the Finger**: The chancre is usually firm, round, small, and painless, appearing at the spot where syphilis entered the body. It lasts three to six weeks and heals on its own. If adequate treatment is not administered, the infection progresses to the secondary stage.

DIAGNOSIS AND TREATMENT

Diagnosis is usually via blood tests, but the bacteria can also be visualized under a microscope. Syphilis can be effectively treated with antibiotics, specifically the preferred intramuscular penicillin G (given intravenously for neurosyphilis), or else ceftriaxone, and in those who have a severe penicillin allergy, oral doxycycline or azithromycin.

Syphilis is believed to have infected 12 million people globally in 1999, with more than 90 percent of cases in the developing world. Rates decreased dramatically after the widespread availability of penicillin in the 1940s. However, rates of infection have increased since the turn of the century in many countries, often in combination with human immunodeficiency virus (HIV). By some accounts, this has been attributed, in part, to unsafe sexual practices among men who have sex with men, increased promiscuity among all genders, prostitution, and decreasing use of barrier protection.

PRIMARY SYPHILIS

Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person. Approximately three to 90 days after the initial exposure (average 21 days) a skin lesion, called a chancre, appears at the point of contact. This chancre is classically a single, firm, painless, non-itchy skin ulceration with a clean base and sharp borders between 0.3 and 3.0 cm in size. However, the lesion may take on almost any form. In the classic form, it evolves from a macule to a papule and finally to an erosion or ulcer. Occasionally, multiple lesions may be present, with multiple lesions more common when co-infected with HIV. Lesions may be painful or tender (in 30 percent of those infected), and they may occur outside of the genitals (2 to 7 percent). The lesion may persist for three to six weeks without treatment.

SECONDARY SYPHILIS

Secondary syphilis occurs approximately four to 10 weeks after the primary infection. While secondary disease is known for the many different ways it can manifest, symptoms most commonly involve the skin, mucous membranes, and lymph nodes. There may be a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles of the feet. The rash may become maculopapular or pustular. It may form flat, broad, whitish, wart-like lesions known as condyloma latum on mucous membranes. All of these lesions harbor bacteria and are infectious.

Other symptoms may include fever, sore throat, malaise, weight loss, hair loss, and headache. Rare manifestations include hepatitis, kidney disease, arthritis, periostitis, optic neuritis, uveitis, and interstitial keratitis. The acute symptoms usually resolve after three to six weeks; however, about 25 percent of people may experience a recurrence of secondary symptoms.

NEUROSYPHILIS

Neurosyphilis occurs when syphilis is left untreated from many years. The brain and spinal cord become infected with the syphilis bacterium, Treponema pallidum, during the secondary stage of infection and can remain latent for 10 to 20 years after the initial infection. Eventually, this infection begins to damage the tissues of the brain and spinal cord, resulting in neurosyphilis. Neurosyphilis is characterized by neurological and psychiatric symptoms, such as confusion, blindness, abnormal gait and dementia. Left untreated, neurosyphilis symptoms will worsen over time and can lead to death. Treatment for neurosyphilis is the same as any other stage of syphilis, requiring only a short course of penicillin.

TRANSMISSION AND PREVENTION

Syphilis is transmitted primarily by sexual contact or during pregnancy from a mother to her fetus. The spirochete is able to pass through intact mucous membranes or compromised skin. Therefore, it is transmissible by kissing, or oral, vaginal, and anal sex. Approximately 30 to 60 percent of those exposed to primary or secondary syphilis will get the disease. It can be transmitted via blood products, but, many countries test for it, and thus the risk is low. The risk of transmission from sharing needles appears limited. Syphilis cannot be contracted through toilet seats, daily activities, hot tubs, or sharing eating utensils or clothing.

As of 2010, there is no vaccine effective for prevention. Abstinence from intimate physical contact with an infected person is effective at reducing the transmission of syphilis, as is the proper use of a latex condom. However, condom use does not completely eliminate the risk.

Key Points

- In addition to sexual contact, syphilis may also be transmitted from mother to child during pregnancy or at birth, resulting in congenital syphilis.

- Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person, and usually presents with a single skin ulceration called a chancre.
- Secondary syphilis occurs approximately four to 10 weeks after the primary infection and may present as a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles of the feet.
- Primary syphilis typically presents with a single skin ulceration called a chancre.
- Neurosyphilis refers to a syphilis infection that affects the central nervous system, and cardiovascular syphilis affects the cardiovascular system.
- Blood tests for syphilis are either treponemal or nontreponemal.
- The Tuskegee syphilis study, where African American men in rural Alabama were told they were receiving free health care and instead were given syphilis in order to study its symptoms and progression, is one of the most infamous cases of questionable medical ethics in US history.

Key Terms

- **congenital syphilis**: syphilis present in utero and at birth
- **Treponema pallidum**: A Gram-negative spirochaete bacterium with subspecies that cause treponemal diseases such as syphilis, bejel, pinta, and yaws.
- **chancre**: A skin lesion, sometimes associated with certain contagious diseases like syphilis.
- **syphilis**: a disease spread via sexual activity, caused by the bacterium Treponema pallidum
- **syphilis**: A disease spread via sexual activity, caused by the bacterium Treponema pallidum.

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15.23G: Genital Ulcer Diseases

Genital ulcers are skin ulcers on the genital area caused by sexually transmitted diseases or noninfectious conditions.

Learning Objectives

- List the causes and symptoms of genital ulcers

Key Points

- The most common STDs that present with genital ulcers are genital herpes, syphilis, chlamydia and chancroid.
- Other than ulceration, enlarged lymph nodes in the groin area may be present, along with blisters and sores.
- To improve the outcome, treatment often starts before identification is complete, with medications chosen based on symptoms and epidemiological circumstances.

Key Terms

- **Behcet's syndrome**: Behcet's syndrome, or Behcet's disease, is an immune disorder that leads to inflammation of the blood vessels. Common symptoms include mouth and genital ulcers, as well as ocular issues.

Genital ulcers are skin ulcers located on the genital area and can be caused by a number of sexually transmitted diseases or other noninfectious conditions such as yeasts, trauma, lupus, rheumatoid arthritis or Behcet's syndrome.

Sexually Transmitted Genital Ulcers

When the reason for a genital ulcer is an infection, it can be caused by a number of sexually transmitted diseases. Among the most common are Herpes simplex virus (HSV), the genital herpes agent; *Treponema pallidum*, that causes syphilis; *Chlamydia trachomatis*, the cause of chlamydia; and *Haemophilus ducreyi*, the chancroid agent. In the United States, the most common reasons for genital ulcers in young and sexually active patients are genital herpes and syphilis.

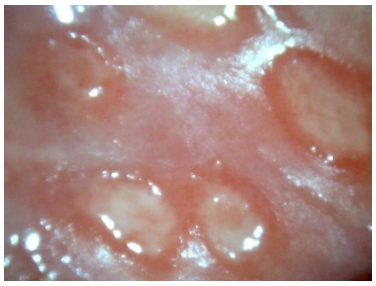

Figure: **Genital Ulcers**: Ulcers caused by genital herpes.

Symptoms and Diagnosis

Genital ulcers can be painful or painless depending on the type of infection. Their appearance can be slightly different from one disease to another. Other than ulceration, enlarged lymph nodes in the groin area can be present, along with blisters and sores. Proper diagnosis cannot be obtained solely through examination and medical history. Testing for a specific infectious agent depends on the likelihood of its presence. In the U.S., testing is recommended for syphilis (by serology and darkfield microscopy) and HSV (culture, serology or PCR), and in cases of chancroid outbreaks or based on the medical history, for the presence of *Haemophilus ducreyi*. In about 25% of the cases, the reason for the ulcer will not be identified by laboratory testing. Syphilis, genital herpes and chancroid have all been associated with increasing the risk for HIV transmission. The CDC recommends routine HIV screening for all patients who present with genital ulcers.

Treatment

Since the ulcers are symptoms of a number of infectious agents, the treatment is chosen according to the disease agent if it can be identified. Quite often, therapy has to start before identification is complete in order to decrease the chances for transmission and to increase the probability of successful treatment. The choice of medication is made, after careful examination of the symptoms and all epidemiological circumstances, based on the most likely causative agent.

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15.23H: Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted disease which causes an infection of the lymph nodes.

Learning Objectives

- Outline the causes and disease stages for lymphogranuloma venereum (LGV)

Key Points

- The infectious agents are a few serovars of Chlamydia trachomatis: L1, L2, L2a, L2b and L3.
- The symptoms of LGV include enlarged and inflamed lymph nodes and lymph passages as well as infection of the surrounding tissues in the genital and abdominal areas.
- Treatment of LGV includes antibiotics and may require drainage of inflamed nodes.

Key Terms

- **serovar**: A group of microorganisms (viruses or bacteria), belonging to the same species, that are characterized by the presence of a specific antigen on their surface.
- **bubo**: An inflamed swelling of a lymph node, especially in the armpit or the groin, due to an infection such as bubonic plague, gonorrhea, tuberculosis or syphilis.

Lymphogranuloma venereum (LGV) is a sexually transmitted disease which was considered rare in the developed world until about a decade ago. LGV is an infection of the lymph nodes. The infectious agent enters the body through breaks in the skin or through the epithelial layer of mucous membranes.

Infectious Agents

The infectious agents are a few serovars of *Chlamydia trachomatis:* L1, L2, L2a, L2b and L3.

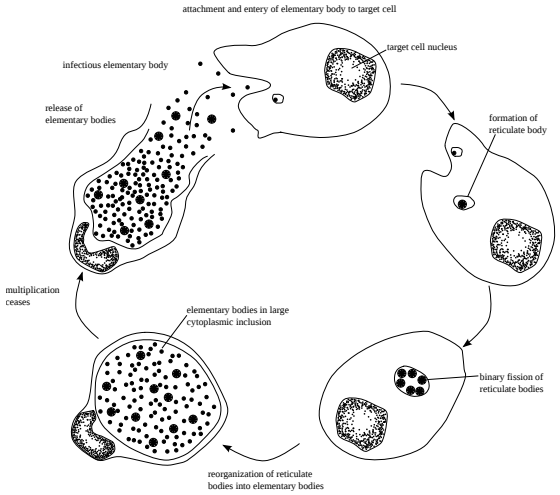

Figure: **Chlamydiae Life Cycle**: Basic diagram of the life cycle of the Chlamydiae. The infectious agents of Lymphogranuloma venereum are a few serovars of Chlamydia trachomatis: L1, L2, L2a, L2b and L3.

Symptoms and Diagnosis

The general symptoms may include fever, malaise and decreased appetite. The disease progresses in stages. In the primary stage, symptoms appear within days after infection. The first symptom is usually painless ulcers at the contact area.The secondary stage can manifest from days to months later. The infectious agent spreads to the lymph nodes through the lymphatic drainage pathways, causing inflammation of the lymph nodes and lymphatic channels. In males with genital infection, these symptoms will usually be in the inguinal or/and femoral areas. In women, an inflammation of the cervix, the fallopian tubes or/and peritonitis may appear as well as inflammation and infection of the lymphatic system. If the infection started in the anal area, it may cause inflammation of the rectum or the colonic mucosa, presenting with symptoms such as anorectal pain, discharge, abdominal cramps and diarrhea.

The enlarged lymph nodes are called buboes and are painful, inflamed and can fixate to the skin. These changes can further progress to necrosis, abscesses and fistulas. As healing starts, fibrosis may occur in the inflamed areas and cause obstruction of the lymphatic system and edema. The fibrosis and edema are considered the third stage of LGV and are mainly permanent. Diagnosis is made after serological analysis and exclusion of other reasons for genital ulcers and lymphatic issues. Culturing is also used for identification of serotypes. Other tests include direct fluorescent antibody analysis (DFA) and PCR tests.

Treatment

Treatment is performed with antibiotics, usually tetracycline, doxycycline or erythromycin. Sometimes drainage of the buboes or abscesses is performed as well. Prognosis is best if treatment starts early in the infection process. Severe complications include bowel obstruction or perforation, which can lead to death.

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15.23I: Group B Streptococcus Colonization

Group B streptococcus is part of the natural microflora in some people, but can sometimes cause life-threatening infections.

Learning Objectives

- Describe the pathogenic characteristics, symptoms and diagnostic test used for Group B streptococcus (GBS)

Key Points

- The most vulnerable groups of people to infection are newborns, the elderly, and people with compromised immune system.
- To prevent infections in infants, many countries routinely screen pregnant women for GBS in the third trimester.
- GBS infection is treated with antibiotics, with penicillin and ampicillin as the primary choice.

Key Terms

- **sepsis**: A life-threatening medical condition caused by a severe inflammatory response of the human body triggered by the presence of an infectious agent.

Group B Streptococcus Colonization

Group B streptococcus (GBS), also called *streptococcus agalactiae* or simply strep B, is part of the natural genital and intestinal microflora in some people. Studies indicate that as many as 40% of women can be carriers. It is usually harmless but under certain circumstances (in newborns, the elderly, and in people with compromised immune systems) it can cause life-threatening infections. The bacteria is gram-positive streptococcus, and possesses the group B antigen from the Lancefield classification. Its infectivity is due to the presence of a antiphagocytic polysaccharide capsule. If a pregnant woman is a carrier of strep B, the baby can become infected during vaginal delivery.

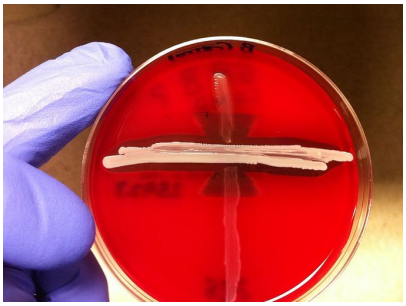

Figure: **The CAMP Test**: The collected sample is streaked on a blood agar plate (vertical streaks) next to staphylococcus aureus culture (horizontal streak). Strep B has weak hemolytic activity, which is enhanced substantially (arrow-like area) when streaked next to s. aureus. The reason for that is the interaction between the CAMP factor from strep B and the s. aureus hemolysin.

Symptoms and diagnosis

Healthy adults are usually asymptomatic carriers of the bacteria. Sometimes it can manifest with urinary tract infections (UTIs) in both pregnant and nonpregnant women. In newborns, the first symptoms are breathing difficulties and pneumonia, which can progress to meningitis and sepsis. In elderly people, it can cause pneumonia and/or UTI and is linked to congestive heart failure. A number of different tests are used as diagnostic tools. Screening pregnant women for GBS, usually in the third trimester, is currently routine in many countries. In the cases of positive status, antibiotics are administered during labor to substantially lower the risk of infection for the baby. This strategy has lead to a significant drop in the rates of infant infection in these countries. A very common diagnostic test is the CAMP test named after the three people that discovered it. Sometimes, before plating, enrichment of the gathered probe is performed. This includes sample growth in special medium that will favor its growth over the other bacteria collected with the specimen. The method of enrichment followed by the CAMP tests is currently the gold standard for GBS diagnosis. It lowers significantly the rates of false negatives. However, culturing takes days and is not feasible if labor starts before screening was completed or in cases when it was not performed at all. The best diagnostic tool will allow identification during labor. PCR techniques are faster but they are still complicated and not fast enough to be used widely for diagnostics once labor has started. TreatmentPregnant women who are carriers of GBS are administered penicillin or ampicillin during labor. These antibiotics are the primary choice for GBS therapy in general, since the bacteria are becoming increasingly resistant to many other common antibiotics.

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15.23J: Chancroid (Soft Chancre)

Chancroid is a sexually transmitted disease caused by *Haemophilus ducreyi*.

Learning Objectives

- Recognize the symptoms, causes and treatment for chancroid

Key Points

- Chancroid is becoming rarer worldwide but there are sporadic outbreaks even in countries where it is uncommon.
- The most common symptoms for chancroid are enlarged lymph nodes and painful, bleeding ulcers with distinctive characteristics.
- Chancroid is treated with single doses of antibiotics like azythromycin or ceftriaxone, or with erythromycin for a week.

Key Terms

- **fastidious**: Microorganisms that are difficult to culture since they need specific nutrients in their medium to grow.
- **lymphadenopathy**: An abnormal enlargement of the lymph nodes

Chancroid (soft chancre) is a sexually transmitted disease and can only be spread through sexual contact. It is becoming rarer worldwide with sporadic outbreaks in countries where it is uncommon. This disease is a risk factor for HIV infection.

Infectious Agent

Chancroid is caused by *Haemophilus ducreyi*, a gram-negative fastidious organism. It enters the body through breaks in the skin.

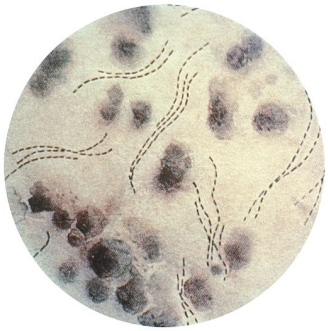

Figure: **Haemophilus ducreyi**: A microscopic image of the bacteria that causes chancroid. The stain used is Gentian Violet and the bacteria are bacilli organized in chains.

Symptoms and Diagnosis

The incubation period of chancroid is between one to fourteen days. The area of infection gets inflamed as cells of the immune system gather to fight the invading organism. Between 30-60% of the patients can also develop lymphadenopathy. Quite often, these enlarged lymph nodes can rupture through the skin and produce draining abscesses.The first symptoms after infection are small painless bumps which quickly become painful ulcers. These ulcers can be quite different in size. The base of the ulcers is usually covered in a gray or yellow substance and bleeds easily. They are typically located in specific ares for men and women. Men often have only one ulcer while women present with multiple ulcers. Women have other symptoms as well such as pain during urination and intercourse. For proper diagnosis, the other two infectious agents that can present with similar although not identical ulcers need to be excluded. Tests for the identification of *Treponema pallidium* (causes syphilis) and HSV (Herpes Simplex Virus, type 2) may be performed to exclude the possibility that ulcers are caused by those agents instead of *Haemophilus ducreyi*. For identification, samples from patients are cultured on chocolate agar. Even though serological and genetic tests can be used for identification, they are not widely used and culturing is the main tool for identifying *Haemophilus ducreyi*.

Treatment

Chancroid is treated with single doses of antibiotics like azythromycin or ceftriaxone, or with erythromycin for a week.

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15.23K: Bacterial Vaginosis

Bacterial vaginosis (BV) is a condition of disrupted balance of the vaginal microflora.

Learning Objectives

- Describe the symptoms, causes and methods of diagnosis for bacterial vaginosis

Key Points

- The most common symptom is white or gray discharge, that can be thin, with fish-like odor (especially strong after intercourse).
- Common bacterial species that can overgrow and cause symptoms of BV are Gardnerella vaginalis, Mobiluncus, Bacteroides and Mycoplasma.
- The treatment regimen is most often metronidizole (for seven days) or clindamycin. BV has high recurrence rates.

Key Terms

- **recurrence**: The returning of a disease that was already treated successfuly.

Bacterial vaginosis (BV) is a condition where the vaginal microflora in women have become disrupted. BV is not a typical sexually transmitted disease since women who have never had sexual contact can suffer from this condition, too. However, having sex with a new partner or multiple partners increases the risk of getting BV but it is unclear how and why that happens. BV is a very common condition and it is estimated that about 1 in 3 women will develop it in their lifetime.

Symptoms and diagnosis

Bacterial vaginosis may be completely asymptomatic. The most common symptom is white or gray discharge, that can be thin, with fish-like odor (especially strong after intercourse). Sometimes itching outside of the vagina or/and burning during urination can also be present. For diagnosis in the clinical practice, a swab from the vaginal wall is obtained and examined with a few different tests called the *Amsel* criteria:

- the discharge should be thin, white, yellow and homogenous
- clue cells must be present in the specimen when observed under the microscope
- pH > 4.5
- the release of fishy odor after the addition of 10% KOH to the specimen

At least three of these tests have to be positive for conclusive diagnosis. Alternative tests can be performed as well and they usually involve Gram staining of the specimen and observing the types of bacteria present in it. Infectious agentsThe normal vaginal microflora contains many species with *Lactobacillus* as the dominant representative. Some *Lactobacilli* produce hydrogen peroxide which can prevent the overgrowth of bacteria that will disturb the balance and cause BV. Some of the bacteria that will produce BV symptoms are *Gardnerella vaginalis*, *Mobiluncus*, *Bacteroides*, and *Mycoplasma*. Factors that are known to disturb the balance are: antibiotics, pH imbalance (douching can alter vaginal pH), psychosocial stress, iron deficiency anemia in pregnant women and women with STD.

Women who already have BV are at increased risk for sexually transmitted diseases including HIV. Bacterial vaginosis during pregnancy increases the risk of premature birth. TreatmentThe treatment regimen is most often *metronidizole* (for seven days) or *clindamycin*. The treatment is usually successful but BV has high rates of recurrence. Treatment of male sex partners is usually not recommended but BV can be transferred to female sex partners.

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15.23L: Chlamydia

Chlamydia infection is a common sexually transmitted infection (STI) in humans caused by the bacterium Chlamydia trachomatis.

Learning Objectives

- Describe the effects of chlamydia in men and women

Key Points

- Chlamydia infection is one of the most common sexually transmitted infections worldwide; it is estimated that about 1 million individuals in the United States are infected with chlamydia.
- Between half and three-quarters of all women who have a chlamydia infection of the cervix (cervicitis) have no symptoms and do not know that they are infected.
- C. trachomatis infection can be effectively cured with antibiotics once it is detected. Current guidelines recommend azithromycin, doxycycline, erythromycin, or ofloxacin.Agents recommended for pregnant women include erythromycin or amoxicillin.

Key Terms

- **azithromycin**: A macrolide antibiotic derived from erythromycin.
- **sexually transmitted disease**: any of various diseases that are usually contracted through sexual contact

Chlamydia infection (from the Greek meaning “cloak”) is a common sexually transmitted infection (STI) in humans caused by the bacterium Chlamydia trachomatis. The term Chlamydia infection can also refer to infection caused by any species belonging to the bacterial family Chlamydiaceae. C. trachomatis is found only in humans.

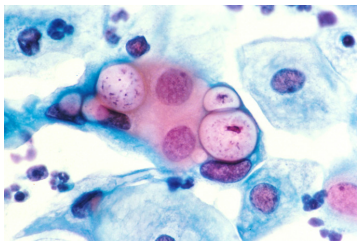

Figure: **Chlamydia**: Pap smear showing C. trachomatis (H&E stain).

Chlamydia is a major infectious cause of human genital and eye disease. Chlamydia infection is one of the most common sexually transmitted infections worldwide; it is estimated that about 1 million individuals in the United States are infected with chlamydia. C. trachomatis is naturally found living only inside human cells. Chlamydia can be transmitted during vaginal, anal, or oral sex, and can be passed from an infected mother to her baby during vaginal childbirth. Between half and three-quarters of all women who have a chlamydia infection of the cervix (cervicitis) have no symptoms and do not know that they are infected. In men, infection of the urethra (urethritis) is usually symptomatic, causing a white discharge from the penis with or without pain on urinating (dysuria).

Occasionally, the condition spreads to the upper genital tract in women (causing pelvic inflammatory disease) or to the epididymis in men (causing epididymitis). If untreated, chlamydial infections can cause serious reproductive and other health problems with both short-term and long-term consequences.

Genital disease

Chlamydial cervicitis in a female patient characterized by mucopurulent cervical discharge, erythema, and inflammation. Male patients may develop a white, cloudy or watery discharge from the tip of the penis.

Women

Chlamydial infection of the neck of the womb (cervicitis) is a sexually transmitted infection which is asymptomatic for about 50-70% of women infected with the disease. The infection can be passed through vaginal, anal, or oral sex. Of those who have an asymptomatic infection that is not detected by their doctor, approximately half will develop pelvic inflammatory disease (PID), a generic term for infection of the uterus, fallopian tubes, and/or ovaries. PID can cause scarring inside the reproductive organs,

which can later cause serious complications, including chronic pelvic pain, difficulty becoming pregnant, ectopic (tubal) pregnancy, and other dangerous complications of pregnancy.Chlamydia is known as the “Silent Epidemic” because in women, it may not cause any symptoms in 75% of cases, and can linger for months or years before being discovered. Symptoms that may occur include unusual vaginal bleeding or discharge, pain in the abdomen, painful sexual intercourse (dyspareunia), fever, painful urination or the urge to urinate more frequently than usual (urinary urgency).

Men

In men, chlamydia shows symptoms of infectious urethritis (inflammation of the urethra) in about 50% of cases. Symptoms that may occur include: a painful or burning sensation when urinating, an unusual discharge from the penis, swollen or tender testicles, or fever. Discharge, or the purulent exudate, is generally less viscous and lighter in color than for gonorrhea. If left untreated, it is possible for chlamydia in men to spread to the testicles causing epididymitis, which in rare cases can cause sterility if not treated within 6 to 8 weeks. Chlamydia is also a potential cause of prostatitis in men, although the exact relevance in prostatitis is difficult to ascertain due to possible contamination from urethritis.

Treatment

C. trachomatis infection can be effectively cured with antibiotics once it is detected. Current guidelines recommend azithromycin, doxycycline, erythromycin, or ofloxacin. Agents recommended for pregnant women include erythromycin or amoxicillin.

An option for treating partners of patients (index cases) diagnosed with chlamydia or gonorrhea is *patient-delivered partner therapy*(PDT or PDPT), which is the clinical practice of treating the sex partners of index cases by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner.

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SECTION OVERVIEW

15.24: Viral Diseases of the Reproductive System

Topic hierarchy

15.24A: Genital Herpes

15.24B: Genital Warts

15.24C: HIV and AIDS

15.24D: Human Papillomavirus (HPV)

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15.24A: Genital Herpes

Herpes genitalis (or genital herpes) refers to a genital infection by Herpes simplex virus.

Learning Objectives

- Recognize the causes and symptoms of herpes simplex virus (HSV) 1 and 2

Key Points

- Although genital herpes is largely believed to be caused by HSV-2, genital HSV-1 infections are increasing and now exceed 50% in certain populations.
- In males, symptoms of genital herpes include lesions that occur on the glans penis, shaft of the penis or other parts of the genital region, on the inner thigh, buttocks, or anus. In females, lesions appear on or near the pubis, labia, clitoris, vulva, buttocks or anus.
- Presently, genital herpes cannot be cured. Moreover, genital herpes can be transmitted by viral shedding prior to and following the visual signs of symptoms. There are however some drugs that can shorten outbreaks and make them less severe or even stop them from happening.

Key Terms

- **acyclovir**: An antiviral drug used in the treatment of genital herpes.
- **viral shedding**: the successful reproduction, expulsion, and host-cell infection caused by virus progeny.

Herpes genitalis (or genital herpes) refers to a genital infection by Herpes simplex virus. Following the classification HSV into two distinct categories of HSV-1 and HSV-2 in the 1960s, it was established that “HSV-2 was below the waist, HSV-1 was above the waist”.

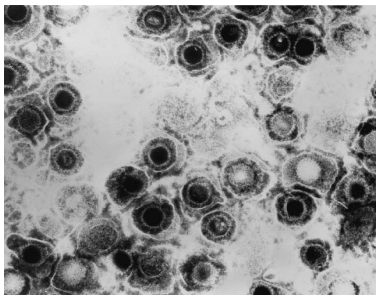

Figure: **Transmission electron micrograph of herpes simplex virus.**: TEM micrograph of a herpes simplex virus.

Although genital herpes is largely believed to be caused by HSV-2, genital HSV-1 infections are increasing and now exceed 50% in certain populations, and that rule of thumb no longer applies. HSV is believed to be asymptomatic in the majority of cases, thus aiding contagion and hindering containment. When symptomatic, the typical manifestation of a primary HSV-1 or HSV-2 genital infection is clusters of genital sores consisting of inflamed papules and vesicles on the outer surface of the genitals, resembling cold sores. These usually appear 4–7 days after sexual exposure to HSV for the first time. Genital HSV-1 infection recurs at rate of about one sixth of that of genital HSV-2.

In males, the lesions occur on the glans penis, shaft of the penis or other parts of the genital region, on the inner thigh, buttocks, or anus. In females, lesions appear on or near the pubis, labia, clitoris, vulva, buttocks or anus. Other common symptoms include pain, itching, and burning. Less frequent, yet still common, symptoms include discharge from the penis or vagina, fever, headache, muscle pain (myalgia), swollen and enlarged lymph nodes and malaise. Women often experience additional symptoms that include painful urination (dysuria) and cervicitis. Herpetic proctitis (inflammation of the anus and rectum) is common for individuals participating in anal intercourse.After 2–3 weeks, existing lesions progress into ulcers and then crust and heal, although lesions on mucosal surfaces may never form crusts. In rare cases, involvement of the sacral region of the spinal cord can cause acute urinary retention and one-sided symptoms and signs of myeloradiculitis (a combination of myelitis and radiculitis): pain, sensory loss, abnormal sensations (paresthesia) and rash. Historically this has been termed Elsberg syndrome, although this entity is not clearly defined.

Treatment

Medical research has not been able to find a way to halt the spread of herpes and the number of infected people keeps growing. In the United States alone, 45 million people are infected, with an additional one million new infections occurring every year. Presently, genital herpes cannot be cured. Moreover, genital herpes can be transmitted by viral shedding prior to and following the visual signs of symptoms. There are however some drugs that can shorten outbreaks and make them less severe or even stop them from happening.

Among these drugs are: acyclovir, valacyclovir and famciclovir.Acyclovir is an antiviral drug used against herpes viruses, varicella-zoster, and Epstein-Barr Viruses. This drug reduces the pain and the number of lesions in the initial case of genital herpes. Furthermore, it decreases the frequency and severity of recurrent infections. It comes in capsules, tablets, suspension, injection, powder for injection, and ointment. The ointment is used topically and it decreases pain, reduces healing time, and limits the spread of the infection.Valacyclovir is also used to treat herpes virus infections. Once in the body, it becomes the anti-herpes medicine, acyclovir. It helps relieve the pain and discomfort and the sores heal faster. It only comes in caplets and its advantage is that it has a longer duration of action than acyclovir. Famciclovir is another antiviral drug that belongs to the same class of acyclovir and valacyclovir. Famciclovir is a prodrug that is converted to penciclovir in the body. The latter is the one active against the viruses. This drug has a longer duration of action than acyclovir and it only comes in tablets.

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15.24B: Genital Warts

Genital warts is a highly contagious sexually transmitted disease caused by some sub-types of human papillomavirus (HPV).

Learning Objectives

- List the causes and various management procedures for genital warts

Key Points

- Warts are the most easily recognized symptom of genital HPV infection, where types 6 and 11 are responsible for 90% of genital warts cases.
- Genital warts spread through direct skin-to-skin contact during oral, genital, or anal sex with an infected partner.
- Genital warts, histopathologically, characteristically rise above the skin surface due to enlargement of the dermal papillae, have parakeratosis and the characteristic nuclear changes typical of HPV infections (nuclear enlargement with perinuclear clearing).
- There is no cure for HPV, but there are methods to treat visible warts, which could reduce infectivity, although there are no trials studying the effectiveness of removing visible warts in reducing transmission.

Key Terms

- **human papillomavirus**: A virus that affects humans, sometimes causing cervical or other cancer; it is sometimes classified as a sexually transmitted disease.

Genital warts (or Condylomata acuminata, venereal warts, anal warts and anogenital warts) is a highly contagious sexually transmitted disease caused by some sub-types of human papillomavirus (HPV). It is spread through direct skin-to-skin contact during oral, genital, or anal sex with an infected partner. Throat, mouth, and eye genital warts can also be transmitted through oral, genital, or anal sex. Warts are the most easily recognized symptom of genital HPV infection, where types 6 and 11 are responsible for 90% of genital warts cases.

Although it is estimated that only a “small percentage” (between 1% and 5%) of those infected with genital HPV develop genital warts, those infected can still transmit the virus. Other types of HPV also cause cervical cancer and probably most anal cancers, however it is important to underline that the types of HPV that cause the overwhelming majority of genital warts are not the same as those that can potentially increase the risk of genital or anal cancer. HPV prevalence at any one time has been observed in some studies at 27% over all sexually active people, rising to 45% between the ages of 14 and 19.

Diagnosis

Genital warts, histopathologically, characteristically rise above the skin surface due to enlargement of the dermal papillae, have parakeratosis and the characteristic nuclear changes typical of HPV infections (nuclear enlargement with perinuclear clearing).

Prevention

Gardasil (sold by Merck & Co.) is a vaccine that protects against human papillomavirus types 16, 18, 6, and 11. Types 6 and 11 cause genital warts, while 16 and 18 cause cervical cancer. The vaccine is preventive, not therapeutic, and must be given before exposure to the virus type to be effective, ideally before the beginning of sexual activity. The vaccine is widely approved for use by young women, it is being tested for young men, and has been approved for males in some areas, such as the UK, the US and Canada.

Management

There is no cure for HPV, but there are methods to treat visible warts, which could reduce infectivity, although there are no trials studying the effectiveness of removing visible warts in reducing transmission. Every year, Americans spend $200 million on the treatment of genital warts. Genital warts may disappear without treatment, but sometimes eventually develop a fleshy, small raised growth. There is no way to predict whether they will grow or disappear.

Warts can sometimes be identified because they show up as white when acetic acid is applied, but this method is not recommended on the vulva because microtrauma and inflammation can also show up as acetowhite. Magnifying glasses or colposcope may also be used to aid in identifying small warts. Depending on the sizes and locations of warts (as well as other factors), a doctor will offer one of several ways to treat them. Podofilox is the first-line treatment due to its low cost.Almost all treatments can potentially

cause depigmentation or scarring. A 0.15% – 0.5% podophyllotoxin (also called podofilox) solution in a gel or cream. Marketed as Condylox (0.5%), Wartec (0.15%) and Warticon (0.15%), it can be applied by the patient to the affected area and is not washed off. It is the purified and standardized active ingredient of the podophyllin (see below). Podofilox is safer and more effective than podophyllin. Skin erosion and pain are more commonly reported than with imiquimod and sinecatechins. Its use is cycled (2 times per day for 3 days then 4–7 days off); one review states that it should only be used for four cycles.

Imiquimod (Aldara) is a topical immune response cream, applied to the affected area. It causes less local irritation than podofilox but may cause fungal infections (11% in package insert) and flu-like symptoms (less than 5% disclosed in package insert). Sinecatechins (marketed as Veregen and Polyphenon E) is an ointment of catechins (55% epigallocatechin gallate) extracted from green tea and other components. Mode of action is undetermined. It appears to have higher clearance rates than podophyllotoxin and imiquimod and causes less local irritation, but clearance takes longer than with imiquimod. Liquid nitrogen cryosurgery is safe for pregnancy. It kills warts 71–79% of the time, but recurrence is 38% to 73% 6 months after treatment. Local infections have been reported. Trichloroacetic acid (TCA) is less effective than cryosurgery, and is not recommended for use in the vagina, cervix, or urinary meatus. Surgical excision is best for large warts, and has a greater risk of scarring. Laser ablation does not seem to be any more effective than other physician-applied methods, but is often used as a last resort and is extremely expensive. A 20% podophyllin anti-mitotic solution, applied to the affected area and later washed off. However, this crude herbal extract is not recommended for use on vagina, urethra, perianal area, or cervix, and must be applied by a physician.

Reported reactions include nausea, vomiting, fever, confusion, coma, renal failure, ileus, and leukopenia; death has been reported with extensive topical application, or application on mucous membranes. Interferon can be used; it is effective, but it is also expensive and its effect is inconsistent. Electrocauterization can be used; it is an older procedure but recovery time is generally longer. In severe cases of genital warts, treatment may require general or spinal anesthesia. This is a surgical procedure. More effective than cryosurgery and recurrence is at a much lower rate. Oral Isotretinoin is a therapy that has proven effective in experimental use, but is rarely used due to potentially severe side effects. In a small-scale study, low dose oral isotretinoin showed considerable efficacy and may represent an alternative systemic form of therapy for Genital Warts. Yet, albeit this indicative evidence not many studies have been conducted to further confirm the findings. In most countries this therapy is currently unapproved and only used as an alternative therapy if other therapies failed.

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15.24C: HIV and AIDS

Human immunodeficiency virus infection/acquired immunodeficiency syndrome is a disease of the human immune system caused by HIV.

Learning Objectives

- Describe the mode of transmission, mechanisms of infection, treatment options, and WHO and CDC classifications for the human immunodeficiency virus (HIV)

Key Points

- During the initial HIV infection a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms.
- HIV is transmitted primarily via unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions and hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding.
- Abacavir, a nucleoside analog reverse transcriptase inhibitor (NARTI or NRTI) is used to treat HIV. Current HAART options are combinations (or “cocktails”) consisting of at least three medications belonging to at least two types, or “classes,” of antiretroviralagents.

Key Terms

- **immunodeficiency**: A depletion in the body’s natural immune system, or in some component of it.
- **AIDS**: an infectious disease, caused by HIV, that causes the gradual degeneration of the body’s immune system

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/ AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). During the initial infection a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses it interferes more and more with the immune system, making people much more likely to get infections, including opportunistic infections, and tumors that do not usually affect people with working immune systems.

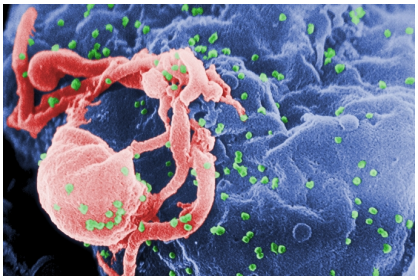

Figure: **HIV-1**: Scanning electron micrograph of HIV-1, colored green, budding from a cultured lymphocyte.

HIV is transmitted primarily via unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions and hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV. Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the spread of the disease. There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and may be associated with side effects.

Virology

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is a retrovirus that primarily infects components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells.HIV is a member of the genus Lentivirus, part of the family of Retroviridae. Lentiviruses share many morphological and biological characteristics. Many species of mammals are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is

then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors. Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may betranscribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew. Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was originally discovered (and initially referred to also as LAV or HTLV-III). It is more virulent, more infective, and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 as compared with HIV-1 implies that fewer people exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.

Classifications of HIV infection

Two main clinical staging systems are used to classify HIV and HIV-related disease for surveillance purposes: the WHO disease staging system for HIV infection and disease, and the CDC classification system for HIV infection. The CDC's classification system is more frequently adopted in developed countries. Since the WHO's staging system does not require laboratory tests, it is suited to the resource-restricted conditions encountered in developing countries, where it can also be used to help guide clinical management. Despite their differences, the two systems allow comparison for statistical purposes.

The World Health Organization first proposed a definition for AIDS in 1986. Since then, the WHO classification has been updated and expanded several times, with the most recent version being published in 2007. The WHO system uses the following categories:

Primary HIV infection: May be either asymptomatic or associated with acute retroviral syndrome.

Stage I: HIV infection is asymptomatic with a CD4+ T cell count (also known as CD4 count) greater than 500/uL. May include generalized lymph node enlargement.

Stage II: Mild symptoms which may include minor mucocutaneous manifestations and recurrent upper respiratory tract infections. A CD4 count of less than 500/uL.

Stage III: Advanced symptoms which may include unexplained chronic diarrhea for longer than a month, severe bacterial infections including tuberculosis of the lung as well as a CD4 count of less than 350/uL.

Stage IV or AIDS: severe symptoms which includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma. A CD4 count of less than 200/uL.

The United States Center for Disease Control and Prevention also created a classification system for HIV, and updated it in 2008. In this system HIV infections are classified based on CD4 count and clinical symptoms, and describes the infection in three stages:

Stage 1: CD4 count ≥ 500 cells/uL and no AIDS defining conditions

Stage 2: CD4 count 200 to 500 cells/uL and no AIDS defining conditions

Stage 3: CD4 count ≤ 200 cells/uL or AIDS defining conditions

Unknown: if insufficient information is available to make any of the above classificationsFor surveillance purposes, the AIDS diagnosis still stands even if, after treatment, the CD4+ T cell count rises to above 200 per µL of blood or other AIDS-defining illnesses are cured.

Antiviral therapy

Abacavir, a nucleoside analog reverse transcriptase inhibitor (NARTI or NRTI) is used to treat HIV. Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes," of antiretroviralagents. Initially treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analogue reverse transcriptase inhibitors(NRTIs). Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC). Combinations of agents which include a protease inhibitors (PI) are used if the above regime loses effectiveness.

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15.24D: Human Papillomavirus (HPV)

Human papillomavirus (HPV) is a virus from the papillomavirus family that is capable of infecting humans.

Learning Objectives

- Discuss the relationship between the human papillomavirus (HPV) and the development of cancer

Key Points

- HPVs establish productive infections only in keratinocytes of the skin or mucous membranes.
- While the majority of the known types of HPV cause no symptoms in most people, some types can cause warts (verrucae), while others can – in a minority of cases – lead to cancers of the cervix, vulva, vagina, penis, oropharynx and anus.
- In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy.
- HPV vaccines (Cervarix and Gardasil), which prevent infection with the HPV types (16 and 18) that cause 70% of cervical cancer, may lead to further decreases in cervical cancer.

Key Terms

- **verrucae**: warts
- **Papanicolaou (Pap) test**: screening of the cervical cells used to detect abnormal cells that may develop into cancer.

Human papillomavirus (HPV) is a virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. While the majority of the known types of HPV cause no symptoms in most people, some types can cause warts (verrucae), while others can – in a minority of cases – lead to cancers of the cervix, vulva, vagina, penis, oropharynx and anus. Recently, HPV has been linked with an increased risk of cardiovascular disease. In addition, HPV 16 and 18 infections are strongly associated with an increased odds ratio of developing oropharyngeal (throat) cancer.

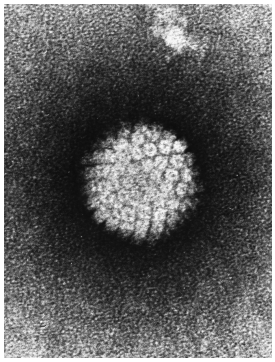

Figure: **EM of HPV**: TEM of papillomavirus.

More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region. Some sexually transmitted HPV types may cause genital warts. Persistent infection with “high-risk” HPV types — different from the ones that cause skin warts — may progress to precancerous lesions and invasive cancer. HPV infection is a cause of nearly all cases of cervical cancer. However, most infections with these types do not cause disease.

Most HPV infections in young females are temporary and have little long-term significance. Seventy percent of infections are gone in 1 year and ninety percent in 2 years. However, when the infection persists — in 5% to 10% of infected women — there is high risk of developing precancerous lesions of the cervix, which can progress to invasive cervical cancer. This process usually takes 10–15 years, providing many opportunities for detection and treatment of the pre-cancerous lesion. Progression to invasive cancer can be almost always prevented when standard prevention strategies are applied, but the lesions still cause considerable burden necessitating preventive surgeries, which do in many cases involve loss of fertility.

In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy. During a colposcopic inspection, biopsies can be taken and abnormal areas can be removed with a simple procedure, typically with a cauterizing loop or,

more commonly in the developing world — by freezing (cryotherapy). Treating abnormal cells in this way can prevent them from developing into cervical cancer.

Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world, but even so there were 11,000 cases and 3,900 deaths in the U.S. in 2008. Cervical cancer has substantial mortality in resource-poor areas; worldwide, there are an estimated 490,000 cases and 270,000 deaths each year.

HPV vaccines (Cervarix and Gardasil), which prevent infection with the HPV types (16 and 18) that cause 70% of cervical cancer, may lead to further decreases.

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SECTION OVERVIEW

15.25: Fungal and Protozoan Diseases of the Reproductive System

Topic hierarchy

15.25A: Vulvovaginal Candidiasis

15.25B: Trichomoniasis

15.25C: The TORCH Panel of Tests

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15.25A: Vulvovaginal Candidiasis

Candidal vulvovaginitis is an infection of the vagina's mucous membranes caused by Candida albicans.

Learning Objectives

- Analyze the symptoms and factors involved in vulvovaginal candidiasis

Key Points

- Up to 75% of women will have this infection at some point in their lives, and approximately 5% will have recurring episodes. It is the second most common cause of vaginal inflammation after bacterial vaginosis.
- The Candida species of fungus is found naturally in the vagina, and is usually harmless.
- It is not known exactly how changes in the vagina trigger thrush, but it may be due to a hormone (chemical) imbalance. In most cases, the cause of the hormonal changes is unknown. Some possible risk factors have been identified, such as taking antibiotics.

Key Terms

- **Candida albicans**: a diploid asexual fungus (a form of yeast). An overgrowth results in candidiasis in immunocompromised patients.
- **vulvovaginal candidiasis**: candidal vulvovaginitis or vaginal thrush is an infection of the vagina's mucous membranes by Candida albicans.

Candidal vulvovaginitis or vaginal thrush is an infection of the vagina's mucous membranes by Candida albicans. Up to 75% of women will have this infection at some point in their lives, and approximately 5% will have recurring episodes. It is the second most common cause of vaginal inflammation after bacterial vaginosis.

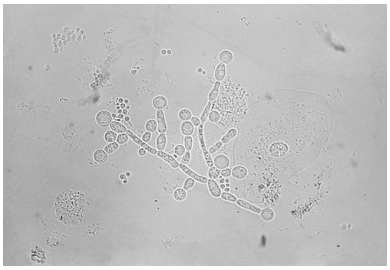

Figure: **Candida albicans**: Tramsmission photomicrograph showing a number of Candida albicans chlamydospores.

It is most commonly caused by a type of fungus known as Candida albicans. The Candida species of fungus is found naturally in the vagina, and is usually harmless. However, if the conditions in the vagina change, Candida albicans can cause the symptoms of thrush. Symptoms of thrush can also be caused by Candida glabrata, Candida krusei, Candida parapsilosis, and Candida tropicalis. Non-albican Candida are commonly found in complicated cases of vaginal thrush such that first line treatment is ineffective. These cases are more likely in immunocompromised patients.

It is not known exactly how changes in the vagina trigger thrush, but it may be due to a hormone (chemical) imbalance. In most cases, the cause of the hormonal changes is unknown. Some possible risk factors have been identified, such as taking antibiotics.

The symptoms of vaginal thrush include vulval itching, vulval soreness and irritation, pain or discomfort during sexual intercourse (superficial dyspareunia), pain or discomfort during urination (dysuria) and vaginal discharge, which is usually odorless. The discharge can be thin and watery, or thick and white, like cottage cheese.

In addition to the above symptoms of thrush, vulvovaginal inflammation can also be present. The signs of vulvovaginal inflammation include erythema (redness) of the vagina and vulva, vagina fissuring (cracked skin), oedema (swelling from a build-up of fluid), also in severe cases, satellite lesions (sores in the surrounding area). This is rare, but may indicate the presence of another fungal condition, or the herpes simplex virus (the virus that causes genital herpes).

While vulvovaginal candidiasis is caused by a the yeast Candida there are many predisposing factors:

- Infection occurs in about 30% of women who are taking a course of oral antibiotics. The evidence of the effect of oral contraceptives is controversial.

- In pregnancy, changes in the levels of female sex hormones, such as estrogen, make a woman more likely to develop a yeast infection. During pregnancy, the Candida fungus is more prevalent (common), and recurrent infection is also more likely.
- Frequency of sexual intercourse appears to be related to the frequency of infections, however infections often occur without sex. Tight-fitting clothing, such as tights and thong underwear, do not appear to increase the risk. Neither do personal hygiene methods.
- Those with poorly controlled diabetes have increased rates of infection while those with well-controlled diabetes do not.
- The risk of developing thrush is also increased in a immunodeficiency, for example, by an immunosuppressive condition, such as HIV or AIDS, or receiving chemotherapy. This is because in these circumstances the body's immune system, which usually fights off infection, is unable to effectively control the spread of the Candida fungus.

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15.25B: Trichomoniasis

Trichomoniasis is primarily an infection of the urogenital tract; the most common site of infection is the urethra and the vagina in women.

Learning Objectives

- Outline the causes and symptoms associated with trichomoniasis

Key Points

- Trichomoniasis is a sexually transmitted disease, and is caused by the single-celled protozoan parasite Trichomonas vaginalis producing mechanical stress on host cells and then ingesting cell fragments after cell death.
- Symptoms usually appear in women within 5 to 28 days of exposure. In many cases, men may hold the parasite for some years without any signs (dormant).
- Trichomoniasis is diagnosed by visually observing the trichomonads via a microscope.

Key Terms

- **trichomoniasis**: A common sexually transmitted disease caused by the parasite Trichomonas vaginalis and infecting the urinary tract or vagina.
- **vaginitis**: Inflammation of the vagina.
- **trichomonads**: flagellate protozoa of the genus Trichomonas.

Trichomoniasis, sometimes referred to as “trich”, is a common cause of vaginitis. It is a sexually transmitted disease, and is caused by the single-celled protozoan parasite Trichomonas vaginalis producing mechanical stress on host cells and then ingesting cell fragments after cell deat. Trichomoniasis is primarily an infection of the urogenital tract; the most common site of infection is the urethra and the vagina in women. Typically, only women experience symptoms associated with Trichomonas infection.

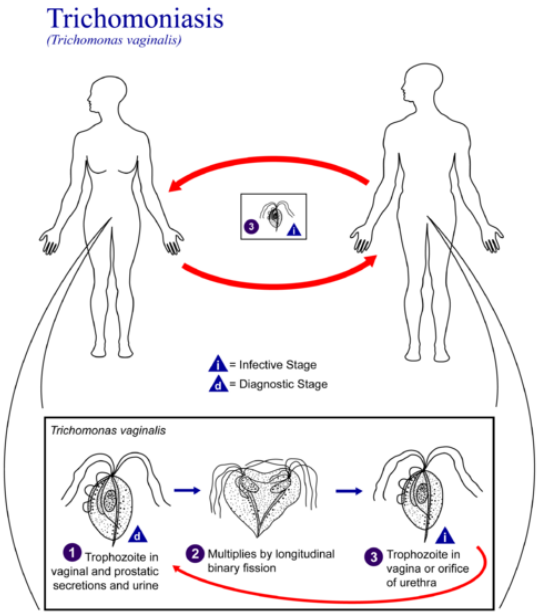

Figure: **Trichomoniasis vaginalis**: Trichomoniasis is primarily an infection of the urogenital tract; the most common site of infection is the urethra and the vagina in women.

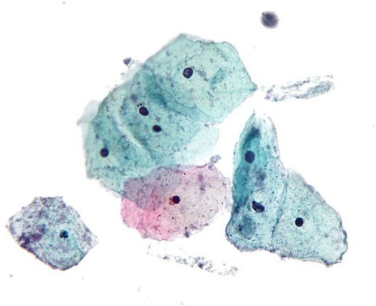

Figure: **Micrograph showing Trichomoniasis**: Micrograph showing a positive result for trichomoniasis. A trichomonas organism is seen on the top-right of the image.

Symptoms include inflammation of the cervix (cervicitis), urethra (urethritis), and vagina (vaginitis) which produces an itching or burning sensation. Discomfort may increase during intercourse and urination. There may also be a yellow-green, itchy, frothy, foul-smelling ("fishy" smell) vaginal discharge. In rare cases, lower abdominal pain can occur. Symptoms usually appear in women within 5 to 28 days of exposure. In many cases, men may hold the parasite for some years without any signs (dormant). Some sexual health specialists have stated that the condition can probably be carried in the vagina for years, despite standard tests being negative. While symptoms are most common in women, some men may temporarily exhibit symptoms such as an irritation inside the penis, mild discharge or slight burning after urination or ejaculation. Trichomoniasis is diagnosed by visually observing the trichomonads via a microscope. In women, the examiner collects the specimen during a pelvic examination by inserting a speculum into the vagina and then using a cotton-tipped applicator to collect the sample. The sample is then placed onto a microscopic slide and sent to a laboratory to be analyzed.

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15.25C: The TORCH Panel of Tests

TORCH infections are a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream from the mother.

Learning Objectives

- Summarize the importance of a TORCH panel of tests

Key Points

- The TORCH complex acronym spells out: T – Toxoplasmosis / Toxoplasma gondii; O – Other infections; R – Rubella; C – Cytomegalovirus; H – Herpes simplex virus.
- TORCH infections cause a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia.
- Symptoms of a TORCH infection may include fever and difficulty feeding, with the newborn often small for their gestational age.

Key Terms

- **haematogenous**: Spread by blood.
- **petechial**: Characterised by, pertaining to, or resembling petechiae (small, nonraised haemorrhages on the skin).
- **TORCH complex**: TORCH complex is a medical acronym for a set of perinatal infections (which are infections that are passed from a pregnant woman to her fetus).

TORCH complex is a medical acronym for a set of perinatal infections (which are infections passed from a pregnant woman to her fetus). TORCH infections can lead to severe fetal anomalies or even fetal loss. They are a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream through the placenta via the chorionic villi. Haematogenous transmission may occur at any time during gestation or occasionally at the time of delivery via maternal-to-fetal transfusion. The TORCH panel is used to screen for certain infectious diseases that can cause birth defects in a baby if the mother contracts them during the pregnancy. The TORCH panel of tests acronym spells out as follows:

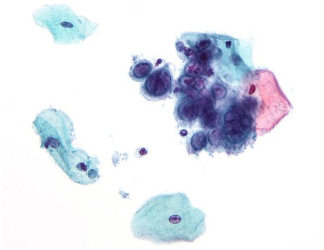

Figure: **Herpes Simplex Virus**: Micrograph of a pap test showing changes (upper-right of image) associated with Herpes Simplex Virus, a TORCH infection.

- T – Toxoplasmosis / Toxoplasma gondii
- O – Other infections
- R – Rubella
- C – Cytomegalovirus
- H – Herpes simplex virus

The “other infections” included under the letter O include Coxsackievirus, Syphilis, Varicella-Zoster Virus, HIV, and Parvovirus B19. Hepatitis B is also sometimes included among “other infections,” but Hepatitis B is a large virus and does not cross the placenta, hence it cannot infect the fetus unless there have been breaks in the maternal-fetal barrier, such as can occur due to bleeding during childbirth or during amniocentesis.

TORCH infections cause a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia. Symptoms of a TORCH infection may include fever and difficultly feeding. The newborn is often small for their gestational age. A petechial rash on the skin may be present, with small reddish or purplish spots due to bleeding from capillaries under the skin. An enlarged liver and spleen (hepatosplenomegaly) is common, as is jaundice. However, jaundice is less common in Hepatitis B because a newborn’s immune system is not developed well enough to mount a response against liver cells,

as would normally be the cause of jaundice in an older child or adult. Hearing impairment, eye problems, mental retardation, autism, and death can be caused by TORCH infections. The TORCH panel is valuable for checking for infections because the mother often has a mild infection with few or no symptoms. It is also possible for genetic conditions (such as Aicardi-Goutieres syndrome) to present in a similar manner.

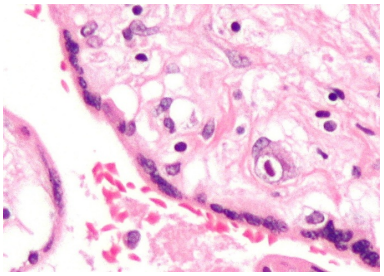

Figure: **Cytomegalovirus infection**: Hematoxylin and Eosin stain showing cytomegalovirus (CMV) infection of the placenta (CMV placentitis), a TORCH infection. The characteristic large nucleus of a CMV infected cell is seen off-center at the bottom-right of the image.

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SECTION OVERVIEW

15.3: Microbial Diseases of the Eye

Topic hierarchy

15.3A: Anatomy of the Eye

15.3B: Normal Eye Microbiota

15.3C: Bacterial Eye Diseases

15.3D: Other Infectious Eye Diseases

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15.3A: Anatomy of the Eye

Many structures in the human eye, such as the cornea and fovea, process light so it can be deciphered by rods and cones in the retina.

Learning Objectives

- Explain how eyes have evolved to benefit organisms

Key Points

- The cornea and the lens bend light to focus the image on the retina; the iris and pupil regulate the amount of light entering the eye.
- The aqueous humour maintains the convex shape of the cornea; the vitreous humour supports the lens and maintains the shape of the entire eye.
- Presbyopia occurs because the image focuses behind the retina; it is similar to hyperopia (farsightedness), which is caused by an eyeball that is too short.
- Myopia (nearsightedness) occurs when an eyeball is elongated; images in the distance appear blurry, but images nearby are clear.
- Rods are used for peripheral and nighttime vision; cones are used for daytime and color vision.
- The fovea is responsible for acute vision because it has a high density of cones.

Key Terms

- **rod**: a rod-shaped cell located in the outer retina of the eye that is extremely sensitive to light
- **retina**: the thin layer of cells at the back of the eyeball where light is converted into neural signals sent to the brain
- **cone**: cell located near the center of the retina that is weakly photosensitive and is responsible for color vision in relatively bright light

Anatomy of the Eye

The retina, a thin layer of cells located on the inner surface of the back of the eye, consists of photoreceptive cells, which are responsible for the transduction of light into nervous impulses. However, light does not enter the retina unaltered; it must first pass through other layers that process it so that it can be interpreted by the retina.

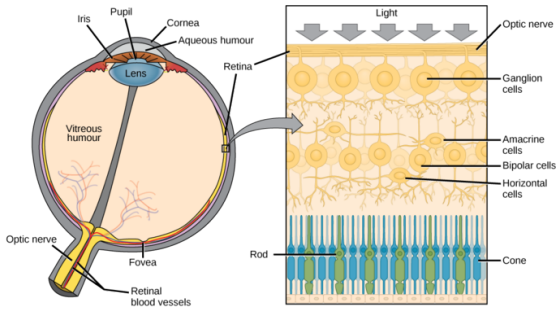

Figure: **Retina**: (a) The human eye is shown in cross section. The human eye contains structures, such as the cornea, iris, lens, and fovea, that process light so it can be deciphered by the retina. Other structures like the aqueous humor and the vitreous humor help maintain the shape of the eye. (b) A blowup shows the layers of the retina. The retina contains photoreceptive cells. In the retina, light is converted into neural signals sent to the brain.

The cornea, the front transparent layer of the eye, along with the crystalline lens, refract (bend) light to focus the image on the retina. After passing through the cornea, light passes through the aqueous humour, which connects the cornea to the lens. This clear gelatinous mass also provides the corneal epithelium with nutrients and helps maintain the convex shape of the cornea. The iris, which is visible as the colored part of the eye, is a circular muscular ring lying between the lens and the aqueous humour that regulates the amount of light entering the eye. Light passes through the center of the iris, the pupil, which actively adjusts its size to maintain a constant level of light entering the eye. In conditions of high ambient light, the iris contracts, reducing the size of the pupil. In conditions of low light, the iris relaxes and the pupil enlarges.

The main function of the lens is to focus light on the retina and fovea centralis. The lens is a transparent, convex structure located behind the cornea. On the other side of the lens is the vitreous humour, which lets light through without refraction, maintains the shape of the eye, and suspends the delicate lens. The lens focuses and re-focuses light as the eye rests on near and far objects in the visual field. The lens is operated by muscles that stretch it flat or allow it to thicken, changing the focal length of light coming through to focus it sharply on the retina. With age comes the loss of the flexibility of the lens; a form of farsightedness called presbyopia results. Presbyopia occurs because the image focuses behind the retina. It is a deficit similar to a different type of farsightedness, hyperopia, caused by an eyeball that is too short. For both defects, images in the distance are clear, but images nearby are blurry. Myopia (nearsightedness) occurs when an eyeball is elongated and the image focus falls in front of the retina. In this case, images in the distance are blurry, but images nearby are clear.

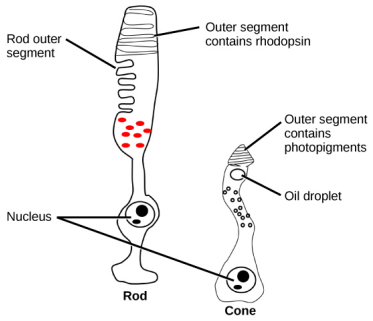

Figure: **Rods and cones**: Rods and cones are photoreceptors in the retina. Rods respond in low light and can detect only shades of gray. Cones respond in intense light and are responsible for color vision.

There are two types of photoreceptors in the retina: rods and cones. Both are named for their general appearance. Rods, strongly photosensitive, are located in the outer edges of the retina. They detect dim light and are used primarily for peripheral and nighttime vision. Cones, weakly photosensitive, are located near the center of the retina. They respond to bright light; their primary role is in daytime, color vision.

The fovea is the region in the center back of the eye that is responsible for acute (central) vision. The fovea has a high density of cones. When you bring your gaze to an object to examine it intently in bright light, the eyes orient so that the object's image falls on the fovea. However, when looking at a star in the night sky or other object in dim light, the object can be better viewed by the peripheral vision because it is the rods at the edges of the retina, rather than the cones at the center, that operate better in low light. In humans, cones far outnumber rods in the fovea.

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15.3B: Normal Eye Microbiota

A small number of bacteria are normally present in the conjunctiva.

Learning Objectives

- Give examples of the microorganisms found in the normal eye microbiota

Key Points

- The lachrymal glands continuously secrete tears keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material.
- Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.
- Some pathogens able to infect the conjunctiva, such as Neisseria gonorrhoeae and Chlamydia trachomatis are thought to have special processes allowing them to attach to the conjunctival epithelium.

Key Terms

- **lachrymal gland**: The lacrimal glands are paired almond-shaped glands, one for each eye, that secrete the aqueous layer of the tear film.
- **conjunctiva**: A clear mucous membrane that lines the inner surface of the eyelid and the exposed surface of the eyeball or sclera.
- **lysozyme**: A bacteriolytic (or antibiotic) enzyme found in many animal secretions and in egg white.

Normal Eye Microbiota

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have been too poorly researched to understand the role they play. Those that are expected to be present and do not cause disease (under normal circumstances), but instead participate in maintaining health, are deemed members of the normal flora.

A small number of bacteria are normally present in the conjunctiva. These include: Chlamydia trachomatis, Chlamydophila pneumoniae, Haemophilus aegyptius, Haemophilus influenzae, Moraxella spp, Neisseria spp, Staphylococcus aureus, Staphylococcus epidermidis and Streptococcus viridians. Staphylococcus epidermidis and certain coryneforms such as Propionibacterium acnes are dominant. Staphylococcus aureus, streptococci, Haemophilus sp. and Neisseria sp. sometimes occur. The lachrymal glands continuously secrete tears keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material. Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.

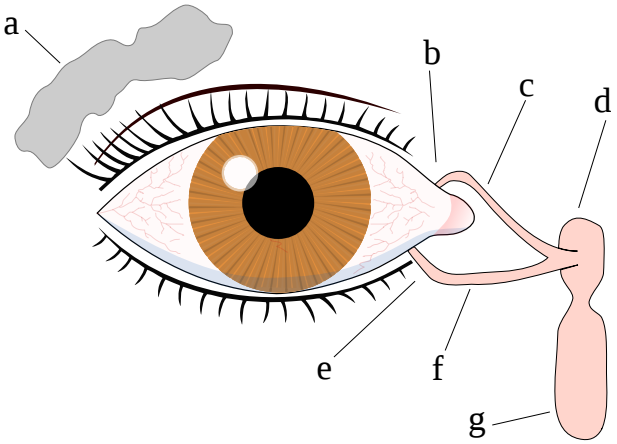

Figure: **The Tear System**: The tear system. Tears are secretions that clean and lubricate the eyes: A) Tear gland/Lacrimal gland, B) Superior lacrimal punctum, C) Superior lacrimal canal lacrimation leads to tears, D) Tear sac/Lacrimal sac, E) Inferior lacrimal punctum, F) Inferior lacrimal canal, G) Nasolacrimal canal.

Some pathogens able to infect the conjunctiva, such as Neisseria gonorrhoeae and Chlamydia trachomatis, are thought to have special processes allowing them to attach to the conjunctival epithelium. Newborn infants are particularly prone to bacterial attachment. Chlamydia and Neisseria may be present in an infected mother and show up on the cervical and vaginal epithelium. In such cases the newborn's eyes may be treated with silver nitrate or antibiotics.

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15.3C: Bacterial Eye Diseases

Conjunctivitis is inflammation of the conjunctiva, most commonly due to an infection.

LEARNING OBJECTIVES

Describe the various causes of conjunctivitis and keratitis and its symptoms

KEY TAKEAWAYS

Key Points

- Classification can be either by extent of the inflamed area or by cause (allergic, bacterial, viral, or chemical).
- Red eye (hyperaemia), irritation (chemosis) and watering (epiphora) of the eyes are symptoms common to all forms of conjunctivitis.
- Keratitis, a condition in which the eye's cornea becomes inflamed, is often marked by moderate to intense pain and usually involves impaired eyesight.

Key Terms

- **conjunctivitis**: An inflammation of the conjunctiva often due to infection.
- **keratitis**: Inflammation of the cornea.

Common Eye Infections

CONJUNCTIVITIS

Conjunctivitis, also called pink eye or Madras eye, is inflammation of the conjunctiva, which consists of the outermost layer of the eye and the inner surface of the eyelids. Conjunctivitis most commonly caused by a viral infection or, less commonly, a bacterial infection, or by an allergic reaction. Classification can be either by extent of the inflamed area or by cause (allergic, bacterial, viral or chemical). Neonatal conjunctivitis is often defined separately due to different organisms.

Symptoms and Diagnosis

An inflamed, red eye (hyperaemia), irritation (chemosis), and watering (epiphora) of the eyes are symptoms common to all forms of conjunctivitis. However, the pupils should be normally reactive and the visual acuity normal. Bacterial conjunctivitis due to common pyogenic (pus-producing) bacteria causes marked grittiness/irritation and a stringy, opaque, greyish or yellowish mucopurulent discharge that may cause the lids to stick together, especially after sleep. Another symptom that could be caused by bacterial conjunctivitis is severe crusting of the infected eye and the surrounding skin.

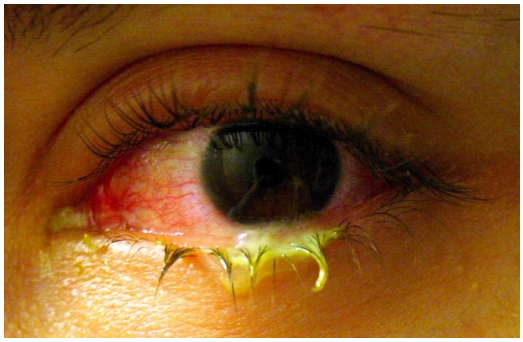

Figure: **Conjunctivitis**: An eye with bacterial conjunctivitis.

Contrary to popular belief, discharge is not essential to the diagnosis. Bacteria such as *Chlamydia trachomatis* or *Moraxella* can cause a non-exudative but persistent conjunctivitis without much redness. The gritty and/or scratchy feeling is sometimes localized enough for patients to insist they must have a foreign body in the eye. The more acute pyogenic infections can be painful. Like viral conjunctivitis, it usually affects only one eye but may spread easily to the other eye.

Corynebacterium diphtheriae causes membrane formation in conjunctiva of non immunized children. Bacterial conjunctivitis usually resolves without treatment. Antibiotics, eye drops, or ointment may only be needed if no improvement is observed after three days.

Chlamydiaconjunctivitis or *trachoma* was once the most important cause of blindness worldwide. The infection can be spread from eye to eye by fingers, shared towels or cloths, coughing and sneezing, and by eye-seeking flies. Newborns can also develop *chlamydia* eye infection through childbirth. *Chlamydia* can affect infants by causing spontaneous abortion, premature birth, and conjunctivitis, which may lead to blindness and pneumonia. Conjunctivitis due to *chlamydia* typically occurs one week after birth (compared with chemical causes (within hours) or gonorrhea (2–5 days)).

KERATITIS

Keratitis is a condition in which the eye's cornea, the front part of the eye, becomes inflamed. The condition is often marked by moderate to intense pain and usually involves impaired eyesight. Superficial keratitis involves the superficial layers (i.e. the epithelium) of the cornea. After healing, this form of keratitis does not generally leave a scar. Deep keratitis involves deeper layers of the cornea (i.e. the epithelium, Bowman's membrane and often stroma), and the natural course leaves a scar upon healing that impairs vision if it occurs on or near the visual axis. This can be reduced or avoided with the use of topical corticosteroid eyedrops.

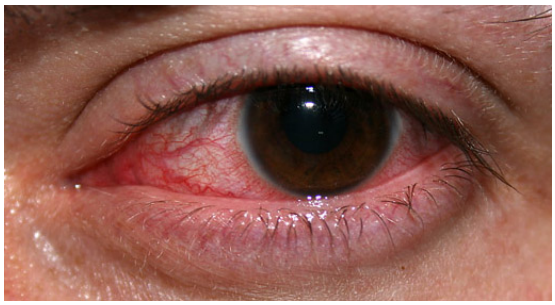

Figure: **Keratitis**: An eye with non-ulcerative sterile keratitis.

Causes and Treatment

Keratitis has multiple causes. Bacterial infection of the cornea can follow from an injury or from result from wearing contact lenses. The bacteria involved are *Staphylococcus aureus* and, for contact lens wearers, *Pseudomonas aeruginosa*. *Pseudomonas aeruginosa* contains enzymes that can digest the cornea. Treatment depends on the cause of the keratitis. Infectious keratitis can progress rapidly, and generally requires urgent antibacterial, antifungal, or antiviral therapy to eliminate the pathogen. Treatment is usually carried out by an ophthalmologist and can involve prescription eye medications, systemic medication, or even intravenous therapy. It is inadvisable to use over-the-counter eye drops as they are typically not helpful in treating infections; using them could also delay crucial correct treatment, increasing the likelihood of sight-threatening complications. In addition, contact lens wearers are typically advised to discontinue contact lens wear and replace contaminated contact lenses and contact lens cases.

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15.3D: Other Infectious Eye Diseases

Fungi and viruses such as herpes simplex can cause eye infections.

LEARNING OBJECTIVES

Summarize the various types of herpes simplex keratitis: dendritic ulcer (epithelial keratitis) and disciform keratitis (stromal keratitis)

KEY TAKEAWAYS

Key Points

- Improper hygiene is a major cause of fungal contamination of contact lenses.
- Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea.
- Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring.

Key Terms

- **ulcer**: An open sore of the skin, eyes, or mucous membrane, often caused by an initial abrasion and generally maintained by an inflammation and/or an infection.
- **keratitis**: Inflammation of the cornea.
- **conjunctivitis**: An inflammation of the conjunctiva often due to infection.

Microbial corneal infection is the most serious and “most common vision threatening” complication of wearing contact lenses, which is believed to be strongly associated with contact lens cases. Such infections “are being increasingly recognized as an important cause of morbidity and blindness” and “may even be life-threatening. ” While the cornea is believed to be the most common site for fungal eye infections, other parts of the eye such as the orbit, sclera, and eyelids may also be involved.

Fungal Infections of the Eye

Factors that contribute to fungal contamination of contact lenses include, but not limited to, hygiene negligence such as: improper sterilization and disinfection of contact lenses, use of contaminated lenses, contaminated contact lens case, contaminated contact lens solution, wearing of contact lenses during eye infections and introduction of micro-organisms from the environment.

Diagnosis is determined”by recognition of typical clinical features and through direct microscopic detection of fungi in scrapes, biopsy specimens, and other samples. “Ultimately, cultures that are made from the samples isolated from patients is what “confirms diagnosis. ” Other tests that may also be used if needed include “histopathological, immunohistochemical, or DNA -based tests. Pathogenesis of the fungal contaminants includes a wide range of factors such as invasiveness, toxigenicity, and host factors. Once diagnosis is accessed, specific anti-fungal therapy can be administered. One of the most popular and common treatments used”for life-threatening and severe ophthalmic mycoses is amphotericin B which is a specific anti-fungal drug. For the treatment for filamentous fungal keratitis, “topical natamycin is usually the first choice. For the treatment of yeast keratitis, topical amphotericin B is usually the first choice. Current advances in further treatments include evaluations of triazoles such as itraconazole and fluconazole” as therapeutic options in ophthalmic mycoses.

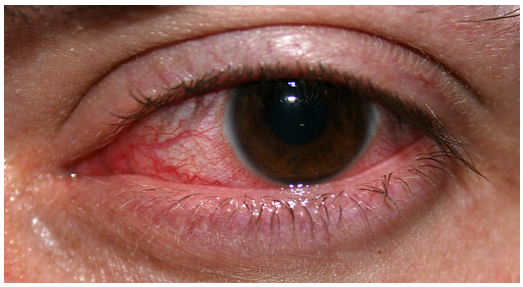

Figure: **Keratitis**: An eye with non-ulcerative sterile keratitis.

Viral Infections of the Eye

Herpes Simplex Virus

Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea. Herpes simplex virus (HSV) infection is very common in humans. HSV is a double-stranded DNA virus that has icosahedral capsid. HSV-1 infections are found more commonly in the oral area and HSV-2 in the genital area. Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection. Corneal involvement is rarely seen in primary infection. Recurrent herpes of the eye in turn is caused by reactivation of the virus in a latently infected sensory ganglion, transport of the virus down the nerve axon to sensory nerve endings, and subsequent infection of ocular surface. The following classification of herpes simplex keratitis is important for understanding this disease:



Figure: **Herpes simplex blepharitis**: Primary eye infection with herpes simplex virus most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection.

Dendritic Ulcer (Epithelial Keratitis)

This classic herpetic lesion consists of a linear branching corneal ulcer (dendritic ulcer). During eye exam the defect is examined after staining with fluorescein dye. The underlying corneal has minimal inflammation. Patients with epithelial keratitis complain of foreign-body sensation, light sensitivity, redness, and blurred vision. Focal or diffuse reduction in corneal sensation develops following recurrent epithelial keratitis. In immune deficient patients or with the use of corticosteroids the ulcer may become large and in these cases it is called geographic ulcer.

Disciform Keratitis (Stromal Kieratitis)

Stromal keratitis manifests as a disc-shaped area of corneal edema. Longstanding corneal edema leads to permanent scarring. It is the major cause of decreased vision associated with HSV. Localized endotheliis (localized inflammation of corneal endothelial layer) is the cause of disciform keratitis.

Diagnostic testing is seldom needed because of its classic clinical features and is not useful in stromal keratitis as there is usually no live virus. Laboratory tests are indicated in complicated cases when the clinical diagnosis is uncertain and in all cases of suspected neonatal herpes infection. Corneal smears or impression cytology specimens can be analyzed by culture, antigen detection, or fluorescent antibody testing. Demonstration of HSV is possible with viral culture. Serologic tests in turn may show a rising antibody titer during primary infection but are of no diagnostic assistance during recurrent episodes.

Treatment of herpes of the eye is different based on its presentation. Epithelial keratitis is caused by live virus. Stromal disease is an immune response. Metaherpetic ulcer results from inability of the corneal epithelium to heal. Epithelial keratitis is treated with topical antivirals, which are very effective with low incidence of resistance. Acyclovir ophthalmic ointment and Trifluridine eye drops have similar effectiveness but are more effective than Idoxuridine and Vidarabine eye drops. Topical antiviral medications are not absorbed by the cornea through an intact epithelium, but orally administered acyclovir penetrates an intact cornea and anterior chamber.

Cytomegalovirus Retinitis

Cytomegalovirus retinitis, also known as CMV retinitis, is an inflammation of the retina of the eye that can lead to blindness. Caused by human cytomegalovirus, it occurs predominantly in people whose immune system has been compromised.

Parasitic Infections of the Eye

Acanthamoeba

Acanthamoeba is a microscopic, free-living ameba (single-celled living organism) commonly found in the environment that can cause rare, but severe, eye illness. Acanthamoeba causes three main types of illness involving the eye (Acanthamoeba keratitis), the brain and spinal cord (Granulomatous Encephalitis), and infections that can spread throughout the entire body (disseminated infection).

Toxoplasma gondii

A single-celled parasite called Toxoplasma gondii causes a disease known as toxoplasmosis. While the parasite is found throughout the world, more than 60 million people in the United States may be infected with the Toxoplasma parasite. Of those who are infected, very few have symptoms because a healthy person's immune system usually keeps the parasite from causing illness.

Signs and symptoms of ocular toxoplasmosis can include reduced vision, blurred vision, pain (often with bright light), redness of the eye, and sometimes tearing. Ophthalmologists sometimes prescribe medicine to treat active disease. Whether or not medication is recommended depends on the size of the eye lesion, the location, and the characteristics of the lesion (acute active, versus chronic not progressing). An ophthalmologist will provide the best care for ocular toxoplasmosis.

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SECTION OVERVIEW

15.4: Microbial Diseases of the Nervous System

Topic hierarchy

15.4A: Functions of the Nervous System

15.4B: Subdivisions of the Nervous System

15.4C: Meningitis

15.4D: Botulism

15.4E: Leprosy

15.4F: Tetanus

15.4G: Paralysis-Causing Bacterial Neurotoxins

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15.4A: Functions of the Nervous System

The primary function of the nervous system is to coordinate and control the various body functions.

Learning Objectives

- Describe the functions of the nervous system

Key Points

- The nervous system is a highly integrated system. The nervous system has three overlapping functions based on sensory input, integration, and motor output.
- At a more integrative level, the primary function of the nervous system is to control and communicate information throughout the body.

Key Terms

- **hormone**: A molecule released by a cell or a gland in one part of the body that sends out messages affecting cells in other parts of the organism.
- **nervous system**: The organ system that coordinates the activities of muscles, monitors organs, constructs and processes data received from the senses, and initiates actions.

The nervous system has three overlapping functions based on the sensory input, integration, and motor output. The nervous system is a highly integrated system.

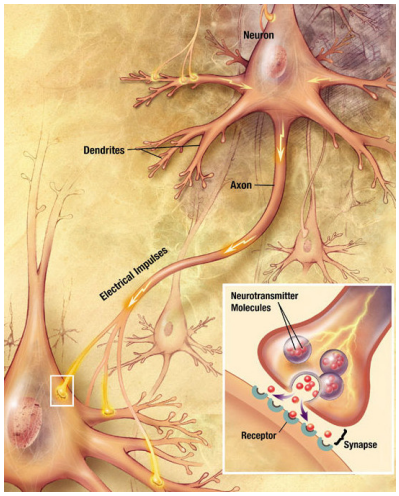

Figure: **Major elements in neuron-to-neuron communication**: Electrical impulses travel along the axon of a neuron. When this signal reaches a synapse, it provokes release of neurotransmitter molecules, which bind to receptor molecules located in the the target cell.

Sensory Input

Sensory input comes from the many sensory receptors that monitor changes occurring both inside and outside the body. The total sum of the information gathered by these receptors is called sensory input. The nervous system processes and interprets sensory input and decides what actions should be taken. The nervous system activates effector organs such as muscles and glands to cause a response called motor output.

Integration

At a more integrative level, the primary function of the nervous system is to control and communicate information throughout the body. It does this by extracting information from the environment using sensory receptors. This sensory input is sent to the central nervous system, which determines an appropriate response.

Motor Response

Once the response is activated, the nervous system sends signals via motor output to muscles or glands to initiate the response.

In humans, the sophistication of the nervous system allows for language, abstract representation of concepts, transmission of culture, and many other features of society that would not otherwise exist.

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15.4B: Subdivisions of the Nervous System

The CNS includes the brain and spinal cord, while the PNS is a network of nerves linking the body to the brain and spinal cord.

Learning Objectives

- Describe the subdivisions of the nervous system

Key Points

- The nervous system is often divided into components called gray matter and white matter. Gray matter contains a relatively high proportion of neuron cell bodies and white matter is composed mainly of axons.
- The peripheral nervous system is subdivided into nerves, the autonomic system, and the somatic system. The autonomic nervous system is further subdivided into the parasympathetic and sympathetic nervous systems.
- The enteric nervous system is an independent subsystem of the peripheral nervous system.
- The central nervous system includes the brain and spinal cord and has various centers that integrate of all the information in the body. These can be subdivided into lower centers that carry out essential body functions and higher centers that control more sophisticated information processing.

Key Terms

- **gray matter**: A major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astroglia and oligodendrocytes), and capillaries.
- **central nervous system**: In vertebrates, the part of the nervous system comprising the brain, brainstem, and spinal cord.
- **white matter**: A region of the central nervous system containing myelinated nerve fibers and no dendrites.
- **peripheral nervous system**: This system consists of the nerves and ganglia outside of the brain and spinal cord.

The nervous system is comprised of two major subdivisions, the central nervous system (CNS) and the peripheral nervous system (PNS).

Central Nervous System

The CNS includes the brain and spinal cord along with various centers that integrate all the sensory and motor information in the body. These centers can be broadly subdivided into lower centers, including the spinal cord and brain stem, that carry out essential body and organ-control functions and higher centers within the brain that control more sophisticated information processing, including our thoughts and perceptions. Further subdivisions of the brain will be discussed in a later section.

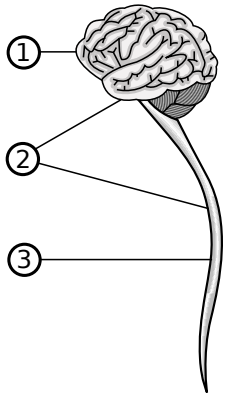

Figure: **The Central Nervous System**: The central nervous system (2) is a combination of the brain (1) and the spinal cord (3).

Gray Matter and White Matter

The nervous system is often divided into components called gray matter and white matter. Gray matter, which is gray in preserved tissue but pink or light brown in living tissue, contains a relatively high proportion of neuron cell bodies. Conversely, white matter is composed mainly of axons and is named because of the color of the fatty insulation called myelin that coats many axons. White

matter includes all of the nerves of the PNS and much of the interior of the brain and spinal cord. Gray matter is found in clusters of neurons in the brain and spinal cord and in cortical layers that line their surfaces.

By convention, a cluster of neuron cell bodies in the gray matter of the brain or spinal cord is called a nucleus, whereas a cluster of neuron cell bodies in the periphery is called a ganglion. However, there are a few notable exceptions to this rule, including a part of the brain called the basal ganglia, which will be discussed later.

Peripheral Nervous System

The PNS is a vast network of nerves consisting of bundles of axons that link the body to the brain and the spinal cord. Sensory nerves of the PNS contain sensory receptors that detect changes in the internal and external environment. This information is sent to the CNS via afferent sensory nerves. Following information processing in the CNS, signals are relayed back to the PNS by way of efferent peripheral nerves.

Autonomic and Somatic Nervous Systems

The PNS is further subdivided into the autonomic nervous system (ANS) and the somatic nervous system. The autonomic system has involuntary control of internal organs, blood vessels, and smooth and cardiac muscles. The somatic system has voluntary control of our movements via skeletal muscle.

As mentioned, the autonomic nervous system acts as a control system and most functions occur without conscious thought. The ANS affects heart rate, digestion, respiratory rate, salivation, perspiration, pupil diameter, urination, and sexual arousal. While most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind. The ANS is classically divided into two subsystems: the parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS).

Parasympathetic and Sympathetic Nervous Systems

Broadly, the parasympathetic system is responsible for stimulation of “rest-and-digest” activities that occur when the body is at rest, including sexual arousal, salivation, lacrimation (tears), urination, digestion, and defecation. The sympathetic nervous syste is responsible for stimulating activities associated with the “fight-or-flight” response: mobilizing the systems of the body for escape or attacking sources of danger. In truth, the functions of both the parasympathetic and sympathetic nervous systems are not so straightforward, but this division is a useful rule of thumb.

The enteric nervous system (ENS) controls the gastrointestinal system and is sometimes considered part of the autonomic nervous system. However, it is sometimes considered an independent system because it can operate independently of the brain and the spinal cord.

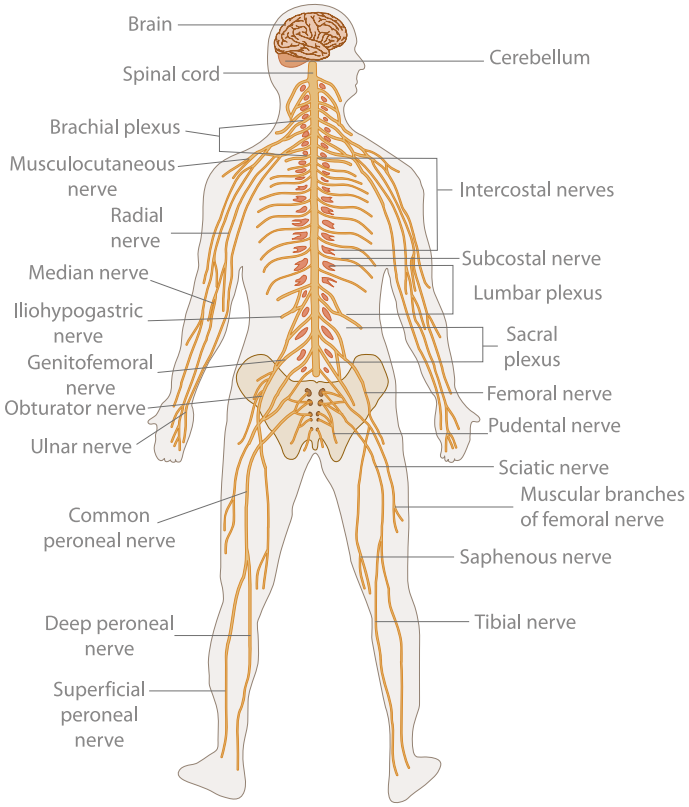

Figure: **The Nervous System of a Vertebrate**: The brain and the spinal cord are the central nervous system (CNS) (shown in yellow). The left-right pair of cranial nerves, spinal nerves, and ganglia make up the peripheral nervous system (shown in dark gold).

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15.4C: Meningitis

Learning Objectives

- Discuss the various causes (viral, bacteria, fungi and protozoa) and modes of transmission for meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs. Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord. Therefore, the condition is classified as a medical emergency.

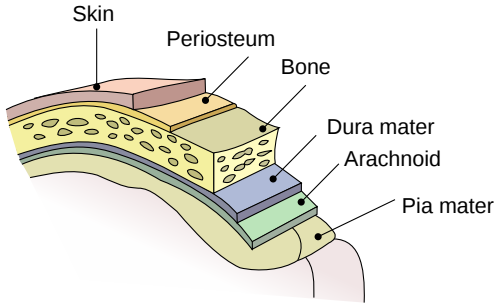

Figure: **The Meninges**: This figure displays the meninges with respect to the skull and surface of the brain.

The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and an inability to tolerate light (photophobia) or loud noises (phonophobia). Children often exhibit only nonspecific symptoms, such as irritability and drowsiness. If a rash is present, it may indicate a particular cause of meningitis. For instance, meningitis caused by the bacterium Neisseria meningitidis (known as "meningococcal menigitis") can be differentiated from meningitis with other causes by a rapidly spreading petechial rash, which may precede other symptoms. The rash consists of numerous small, irregular purple or red spots ("petechiae") on the trunk, lower extremities, mucous membranes, conjuctiva, and (occasionally) the palms of the hands or soles of the feet. Meningococcal bacteria may be accompanied by a characteristic rash. Seizures may also occur for various reasons. In children, seizures are common in the early stages of meningitis and do not necessarily indicate an underlying cause.

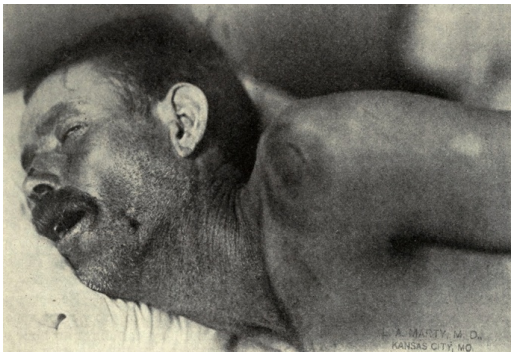

Figure: **Neck stiffness**: Neck stiffness, Texas meningitis epidemic of 1911–12. Nuchal rigidity occurs in 70% of bacterial meningitis in adults.

Meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus, and cognitive deficits, especially if not treated quickly. Some forms of meningitis (such as those associated with meningococci, Haemophilus influenzae type B, pneumococci, or mumps virus infections) may be prevented by immunization.

Meningitis is typically caused by an infection with microorganisms. Most infections are due to viruses (such as enteroviruses or herpes simplex virus), with bacteria (for example group B streptococci), fungi, and protozoa being the next most common causes. It may also result from various non-infectious causes. The term aseptic meningitis refers to cases of meningitis in which no bacterial infection can be demonstrated. This type of meningitis is usually caused by viruses, but it may be due to bacterial infection that has already been partially treated, when bacteria disappear from the meninges, or pathogens infect a space adjacent to the meninges (e.g. sinusitis). Endocarditis (an infection of the heart valves which spreads small clusters of bacteria through the bloodstream) may

cause aseptic meningitis. Aseptic meningitis may also result from infection with spirochetes, a type of bacteria that includes Treponema pallidum (the cause of syphilis) and Borrelia burgdorferi (known for causing Lyme disease).

A lumbar puncture diagnoses or excludes meningitis. A needle is inserted into the spinal canal to extract a sample of cerebrospinal fluid (CSF) which envelops the brain and spinal cord. The CSF is examined in a medical laboratory. In someone suspected of having meningitis, blood tests are performed for markers of inflammation (e.g. C-reactive protein, complete blood count) as well as blood cultures.

The first treatment in acute meningitis consists of antimicrobial and sometimes antiviral therapy. In addition, corticosteroids can also be used to prevent complications from excessive inflammation. The introduction of pneumococcal vaccine has lowered rates of pneumococcal meningitis in both children and adults. Recent skull trauma potentially allows nasal cavity bacteria to enter the meningeal space. Similarly, devices in the brain and meninges such as cerebral shunts carry an increased risk of meningitis.

Bacterial and viral meningitis are contagious and can be transmitted through droplets of respiratory secretions during close contact such as kissing, sneezing, or coughing on someone, but cannot be spread by only breathing the air where a person with meningitis has been. Since the 1980's, many countries have included immunization against Haemophilus influenzae type B in their routine childhood vaccination schemes. This has practically eliminated this pathogen as a cause of meningitis in young children in those countries.

Key Points

- Meningitis can be caused by viruses, bacteria, fungi, and protozoa.
- The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and an inability to tolerate light (photophobia) or loud noises (phonophobia).
- A lumbar puncture diagnoses or excludes meningitis.
- The first treatment in acute meningitis consists of antimicrobial and sometimes antiviral therapy.

Key Terms

- **meninges**: The three membranes that envelop the brain and spinal cord.
- **meningitis**: Inflammation of the meninges, characterized by headache, neck stiffness and photophobia and also fever, chills, vomiting, and myalgia.
- **lumbar puncture**: A diagnostic and at times therapeutic procedure performed to collect a sample of cerebrospinal fluid for biochemical, microbiological, and cytological analysis, or rarely to relieve increased intracranial pressure.

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15.4D: Botulism

Learning Objectives

- Compare and contrast the three major modes of entry for Botulinium toxin (infant botulism or adult intestinal toxemia, foodborne botulism, and wound botulism) and describe its mechanism of action

Overview of Botulism

Botulism is a rare, but sometimes fatal, paralytic illness caused by botulinum toxin. It can affect a wide range of mammals, birds and fish. This toxin is a protein produced under anaerobic conditions by the bacterium Clostridium botulinum. The toxin enters the human body in one of three ways: by colonization of the digestive tract by the bacterium in children (infant botulism) or adults (adult intestinal toxemia), by ingestion of toxin from foods (foodborne botulism), or by contamination of a wound by the bacterium (wound botulism). Person-to-person transmission of botulism does not occur. All forms lead to paralysis that typically starts with the muscles of the face and then spreads towards the limbs. In severe forms, it leads to paralysis of the breathing muscles and causes respiratory failure. In light of this life-threatening complication, all suspected cases of botulism are treated as medical emergencies, and public health officials are usually involved to prevent further cases from the same source. Botulism can be prevented by killing the spores by pressure cooking or autoclaving at 121 °C (250 °F) for 30 minutes or providing conditions that prevent the spores from growing. Additional precautions for infants include not feeding them honey.



Figure: **Botulism**: A 14-year-old with botulism. Note the bilateral total ophthalmoplegia with ptosis in the left image and the dilated, fixed pupils in the right image. This child was fully conscious.

C. botulinum is an anaerobic, Gram positive, spore-forming rod. Botulinium toxin is one of the most powerful known toxins: about one microgram is lethal to humans. It acts by blocking nerve function (neuromuscular blockade) through inhibition of the release of the excitatory neurotransmitter acetyl choline from the presynaptic membrane of neuromuscular junctions in the somatic nervous system. This causes paralysis. Advanced botulism can cause respiratory failure by paralyzing the muscles of the chest, which can progress to respiratory arrest. In all cases, illness is caused by the botulinium toxin produced by the bacterium C. botulinum in anaerobic conditions, and not by the bacterium itself. The pattern of damage occurs because the toxin affects nerves that fire (depolarize) at a higher frequency first.

MODES OF ENTRY

Three main modes of entry for the toxin are known. The most common form in Western countries is infant botulism. This occurs in small children who are colonized with the bacterium during the early stages of their lives. The bacterium then releases the toxin into the intestine, which is absorbed into the bloodstream. The consumption of honey during the first year of life has been identified as a risk factor for infant botulism and it is a factor in a fifth of all cases. The adult form of infant botulism is termed adult intestinal toxemia, and is exceedingly rare. Foodborne botulism results from contaminated foodstuffs in which C. botulinum spores have been allowed to germinate in anaerobic conditions. This typically occurs in home-canned food substances and fermented uncooked dishes. Given that multiple people often consume food from the same source, it is common for more than a single person to be affected simultaneously. Symptoms usually appear 12–36 hours after eating, but can also appear within 6 hours to 10 days. Wound botulism results from the contamination of a wound with the bacteria, which then secrete the toxin into the bloodstream. This has become more common in intravenous drug users since the 1990s, especially people using black tar heroin and those injecting heroin into the skin rather than the veins

TREATMENT

The only drug currently available to treat infant botulism is Botulism Immune Globulin Intravenous-Human (BIG-IV or BabyBIG). BabyBIG was developed by the Infant Botulism Treatment and Prevention Program at the California Department of Public Health. There are two primary Botulinum Antitoxins available for treatment of wound and foodborne botulism. Trivalent (A,B,E) Botulinum Antitoxin is derived from equine sources utilizing whole antibodies (Fab & Fc portions). This antitoxin is available from the local health department via the CDC. The second antitoxin is heptavalent (A,B,C,D,E,F,G) Botulinum Antitoxin which is derived from “despeciated” equine IgG antibodies which have had the Fc portion cleaved off leaving the F(ab’)2 portions. This is a less immunogenic antitoxin that is effective against all known strains of botulism where not contraindicated. This is available from the US Army.

Key Points

- The toxin (s) enters the human body by colonization of the digestive tract by the bacterium, by ingestion of toxin from foods or by contamination of a wound by the bacterium.
- All forms lead to paralysis that typically starts with the muscles of the face and then spreads towards the limbs.
- Botulism can be prevented by killing the spores by pressure cooking or autoclaving at 121 °C (250 °F) for 30 minutes or providing conditions that prevent the spores from growing.

Key Terms

- **infant botulism**: poisoning caused by the toxin from Clostridium botulinum where the gastro-intestinal tract is colonized by spores prior to the protective intestinal bacterial flora having developed
- **spore**: A thick resistant particle produced by a bacterium or protist to survive in harsh or unfavorable conditions.
- **botulism**: Poisoning caused by the toxin from Clostridium botulinum, a type of anaerobic bacteria that grows in improperly-prepared food.
- **wound botulism**: poisoning caused by the toxin from Clostridium botulinum when spores enter a wound under the skin, and, in the absence of oxygen are activated and release toxin
- **toxin**: A toxic or poisonous substance produced by the biological processes of biological organisms.

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15.4E: Leprosy

Learning Objectives

- Describe the causative agents of leprosy: Mycobacterium leprae and Mycobacterium lepromatosis

Leprosy, also known as Hansen's disease (HD), is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract. Skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.

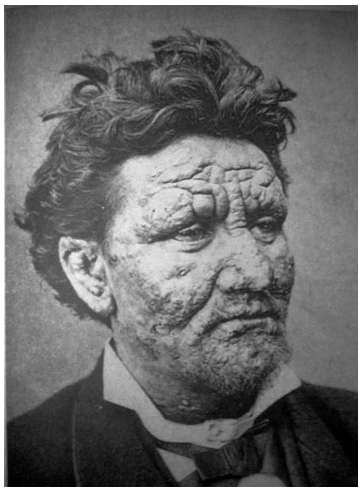

Figure: **Leprosy**: A 23-year-old man infected with leprosy.

Diagnosis

Diagnosis in the U.S. is often delayed because healthcare providers are unaware of leprosy and its symptoms. Early diagnosis and treatment prevents nerve involvement, the hallmark of leprosy, and the disability it causes. There are many kinds of leprosy, but there are common symptoms, including:

- Runny nose
- Dry scalp
- Eye problems
- Skin lesions
- Muscle weakness
- Reddish skin
- Smooth, shiny, diffuse thickening of skin on the face, ears, and hands
- Loss of sensation in fingers and toes
- Thickening of peripheral nerves
- Flat nose due to destruction of nasal cartilage

There is also phonation and resonation of sound during speech. Often there is atrophy of the testes and impotency.

Causative Agents

Mycobacterium leprae and *Mycobacterium lepromatosis* are the causative agents of leprosy. *M. lepromatosis* is a comparatively recently identified mycobacterium that was isolated from a fatal case of diffuse lepromatous leprosy in 2008. An intracellular, acid-fast bacterium, *M. leprae* is aerobic and rod-shaped, and is surrounded by the waxy cell membrane coating characteristic of Mycobacterium species. Due to extensive loss of genes necessary for independent growth, *M. leprae* and *M. lepromatosis* are obligate pathogens, and are unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates. The use of non-culture-based techniques such as molecular genetics has allowed for alternative establishment of causation.

Routes of Infection

M. leprae is usually spread from person to person in respiratory droplets. Studies have shown that leprosy can be transmitted to humans through contact with armadillos, too. Leprosy is not known to be either sexually transmitted or highly infectious after treatment. Approximately 95% of people are naturally immune, and sufferers are no longer infectious after as little as two weeks of treatment. In 1988, Jacinto Convit was nominated for the Nobel Prize in Medicine for developing a vaccine to fight leprosy using a combination of tuberculosis (TB) vaccines with Mycobacterium Leprae. A number of synthetic pharmaceuticals that are effective against leprosy have now been identified, allowing doctors a flexible choice of treatments.

Key Points

- Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.
- M. leprae and M. lepromatosis are obligate pathogens, and are unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates.
- There is now a vaccination and extensive pharmaceutical options for treatment and prevention of leprosy.

Key Terms

- **leprosy**: Leprosy, also known as Hansen's disease (HD), is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis.
- **mycobacterium**: Any of many rod-shaped, aerobic bacteria, of the genus Mycobacterium, that cause diseases such as tuberculosis and leprosy

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15.4F: Tetanus

Tetanus is a medical condition characterized by a prolonged contraction of skeletal muscle fibers.

Learning Objectives

- Describe the mode of transmission and mechanism of action for *Clostridium tetani*

Key Points

- Infection generally occurs through wound contamination and often involves a cut or deep puncture wound.
- There are currently no blood tests that can be used to diagnose tetanus.
- Tetanus can be prevented by vaccination with tetanus toxoid.

Key Terms

- **tetanus**: A serious and often fatal disease caused by the infection of an open wound with the anaerobic bacterium Clostridium tetani, found in soil and the intestines and feces of animals.
- **opisthotonos**: A tetanic spasm in which the body is bent backwards and stiffened.
- **neurotoxin**: A toxin that specifically acts upon neurons, their synapses, or the nervous system in its entirety.
- **tetanospasmin**: The A-B toxin produced by C. tetani which is responsible for the symptoms of tetanus.

Overview

Tetanus is a medical condition characterized by a prolonged contraction of skeletal muscle fibers. The primary symptoms are caused by tetanospasmin, a neurotoxin produced by the Gram-positive, rod-shaped, obligate anaerobic bacterium *Clostridium tetani*.

Infection and Symptomatic Effects

Infection generally occurs through wound contamination and often involves a cut or deep puncture wound. C. tetani is not invasive, and the infection is normally confined to a wound. Here the bacteria multiply and produce tetanospasmin, which is able to travel throughout the body. Tetanospasmin is an A-B toxin. The B subunit binds to the receptors on motor neurons, while the A subunit induces endocytosis to enter the neuron. Early symptoms of the disease include restlessness, irritability and difficulty swallowing. As the infection progresses, muscle spasms develop in the jaw (thus the name “lockjaw”) and elsewhere in the body. Infection can be prevented by proper immunization and by post-exposure prophylaxis. Tetanus often begins with mild spasms in the jaw muscles (lockjaw). The spasms can also affect the chest, neck, back, and abdominal muscles. Back muscle spasms often cause arching, called opisthotonos. Prolonged muscular action causes sudden, powerful, and painful contractions of muscle groups. This is called tetany.



Figure: **Opisthotonus**: Muscular spasms (specifically opisthotonos) in a patient suffering from tetanus. Painting by Sir Charles Bell, 1809.

Tetanus affects skeletal muscle, a type of striated muscle used in voluntary movement. The other type of striated muscle, cardiac or heart muscle, is not affected by the toxin because of its intrinsic electrical properties. The incubation period of tetanus can be long, and may be as long several months, but is usually about eight days. In general, the further the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the more severe the symptoms.

Sources of Infection

Tetanus is often associated with rust, especially rusty nails, but this concept is somewhat misleading. Objects that accumulate rust are often found outdoors, or in places that harbor anaerobic bacteria, but the rust itself does not cause tetanus nor does it contain *C. tetani* bacteria. The rough surface of rusty metal merely provides a prime habitat for a *C. tetani* endospore to reside, and the nail affords a means to puncture skin and deliver endospore into the wound. An endospore is a non-metabolizing survival structure that begins to metabolize and cause infection once in an adequate environment. Because *C. tetani* is an anaerobic bacterium, it and its endospores survive well in an environment that lacks oxygen. Hence, stepping on a nail, rusty or not, may result in a tetanus infection, as the low-oxygen (anaerobic) environment is provided by the same object that causes a puncture wound, delivering endospores to a suitable environment for growth.

Diagnosis, Treatment, and Prevention

There are currently no blood tests that can be used to diagnose tetanus. The diagnosis is based on the presentation of tetanus symptoms. Diagnosis does not depend upon isolation of the bacteria, which is recovered from the wound in only 30% of cases and can be isolated from patients without tetanus. The “spatula test” is a clinical test for tetanus that involves touching the posterior pharyngeal wall with a sterile, soft-tipped instrument, and observing the effect. A positive test result is the involuntary contraction of the jaw (biting down on the “spatula”); a negative test result would normally be a gag reflex attempting to expel the foreign object.

Unlike many infectious diseases, recovery from naturally acquired tetanus does not usually result in immunity to tetanus. This is due to the extreme potency of the tetanospasmin toxin; even a lethal dose of tetanospasmin is insufficient to provoke an immune response.Tetanus can be prevented by vaccination with tetanus toxoid. The CDC recommends that adults receive a booster vaccine every ten years, and standard care practice in many places is to give the booster to any patient with a puncture wound who is uncertain of when he or she was last vaccinated, or if he or she has had fewer than three lifetime doses of the vaccine. The booster may not prevent a potentially fatal case of tetanus from the current wound as it can take up to two weeks for tetanus antibodies to form.

A person infected with *C. tetani* can be treated with antibiotics, which will kill the multiplying bacteria but will have no effect on the endospores or the toxin. To combat the effects of the toxin, tetanus immune globulin (TIG) antitoxin can be given to the patient. These antibodies are able to neutralize the tetanospasmin if they are not already bound to motor neurons, and can confer passive immunity.

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15.4G: Paralysis-Causing Bacterial Neurotoxins

Botulinum toxin is a protein and neurotoxin, which blocks neuromuscular transmission through decreased acetylcholine release.

Learning Objectives

- Describe the mechanism of action for botulinum toxin

Key Points

- Botulinum toxin is produced by Clostridium botulinum, C. butyricum, C. baratii and C. argentinense.
- The light chain of botulinum toxin is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane and releasing acetylcholine.
- The heavy chain of the toxin is particularly important for targeting the toxin to specific types of axon terminals.

Key Terms

- **neurotoxin**: A toxin that specifically acts upon neurons, their synapses, or the nervous system in its entirety.
- **acetylcholine**: A neurotransmitter in humans and other animals. It is an ester of acetic acid and choline with chemical formula CH3COOCH2CH2N⁺(CH3)3.
- **axon**: A nerve fibre, which is a long slender projection of a nerve cell, and which conducts nerve impulses away from the body of the cell to a synapse.

Botulinum toxin is a protein and neurotoxin produced by Clostridium botulinum, C. butyricum, C. baratii and C. argentinense. Botulinum toxin can cause botulism, a serious and life-threatening illness in humans and animals. In 1949, Arnold Burgen's group discovered, through an elegant experiment, that botulinum toxin blocks neuromuscular transmission through decreased acetylcholine release. In 1973, Alan Scott used botulinum toxin type A (BTX-A) in monkey experiments. In 1980, he officially used BTX-A for the first time in humans to treat "crossed eyes" (strabismus), a condition in which the eyes are not properly aligned with each other, as well as "uncontrollable blinking" (blepharospasm). In 1993, Pasricha and colleagues showed that botulinum toxin could be used for the treatment of achalasia, a spasm of the lower esophageal sphincter. In 1994, Bushara showed botulinum toxin injections inhibit sweating; this was the first demonstration of non-muscular use of BTX-A in humans. The cosmetic effect of BTX-A on wrinkles was first reported by J. D. and J. A. Carruthers in a 1992 study on BTX-A for the treatment of glabellar frown lines. The acceptance of BTX-A use for the treatment of muscle pain disorders is growing, with approvals pending in many European countries. The efficacy of BTX-A in treating a variety of other medical conditions (including prostatic dysfunction, asthma, and others) is an area of continued study.

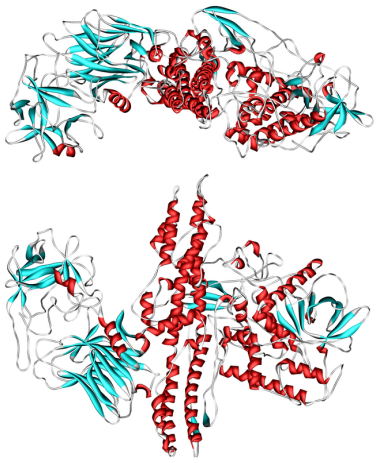

Figure: **Botulinum Toxin**: Structure of Botulinum toxin, a protein and neurotoxin produced by the bacterium Clostridium botulinum

Foodborne botulism can be transmitted through food that has not been heated correctly prior to being canned, or food from a can that has not been cooked correctly. Most infant botulism cases cannot be prevented because the bacteria that cause this disease are in soil and dust. The bacteria can also be found inside homes on floors, carpet, and countertops, even after cleaning. Honey can contain the bacteria that cause infant botulism, so children less than 12 months old should not be fed honey.

Botulinum toxin is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane to release acetylcholine. By inhibiting acetylcholine release, the toxin interferes with nerve impulses and causes flaccid (sagging) paralysis of muscles in botulism, as opposed to the spastic paralysis seen in tetanus. The heavy chain of the toxin is particularly important for targeting the toxin to specific types of axon terminals. The toxin must get inside the axon terminals to cause paralysis. Following the attachment of the toxin heavy chain to proteins on the surface of axon terminals, the toxin can be taken into neurons by endocytosis. The light chain is able to cleave endocytotic vesicles and reach the cytoplasm. The light chain of the toxin has protease activity. The type A toxin proteolytically degrades the SNAP-25 protein, a type of SNARE protein. The SNAP-25 protein is required for vesicle fusion that releases neurotransmitters from the axon endings (in particular acetylcholine). Botulinum toxin specifically cleaves these SNAREs, and so prevents neurosecretory vesicles from docking/fusing with the nerve synapse plasma membrane and releasing their neurotransmitters.

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SECTION OVERVIEW

15.5: Other Diseases of the Nervous System

Topic hierarchy

15.5A: Rabies

15.5B: Poliomyelitis

15.5C: Hantavirus

15.5D: Arboviral Encephalitis

15.5E: Rickettsial Diseases

15.5F: Lyme Disease

15.5G: West Nile Virus

15.5H: Plague

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15.5A: Rabies

Rabies is a viral disease that causes acute encephalitis in warm-blooded animals.

Learning Objectives

- Examine the causes and symptoms associated with infection by the rabies virus

Key Points

- The rabies virus infects the central nervous system, travelling from the peripheral nerves to the brain.
- Symptoms include hydrophobia, paranoia, terror, mania, hallucinations, and delirium.
- Once symptoms have presented, survival is rare, but treatment administered before the onset of symptoms is highly successful.

Key Terms

- **hydrophobia**: An aversion to water, as a symptom of rabies.
- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.

Rabies is a viral disease that causes acute encephalitis (inflammation of the brain) in warm-blooded animals. Rabies literally means "madness" in Latin. The disease is zoonotic and can be transmitted from one species to another, commonly by a bite from an infected animal. In humans, rabies is almost invariably fatal if postexposure prophylaxis is not administered prior to the onset of severe symptoms.



Figure: **Rabies Patient**: Rabies symptoms include malaise, violent movements, terror, mania, and delirium.

The rabies virus infects the central nervous system, travelling from the peripheral nerves to the brain. In humans, the incubation period between infection and the first sign of symptoms is typically two to 12 weeks, although periods as short as four days and longer than six years have been documented. Incubation period depends on the quantity of virus introduced and the distance it must travel to reach the central nervous system. Once there, symptoms begin to show and the infection is virtually untreatable. Early-stage symptoms include malaise, headache and fever, violent movements, uncontrolled excitement, depression, confusion, agitation, anxiety, and hydrophobia. Late stage symptoms extend to paranoia, terror, mania, and hallucinations progressing into delirium. Once symptoms have presented, survival is rare. Death almost invariably occurs within two to 10 days. Treatment with human rabies immunoglobulin (HRIG) and rabies vaccine is highly successful if administered before the onset of symptoms.



Figure: **Rabid Dog**: Close-up of a dog's face during late-stage "dumb" paralytic rabies. Animals with "dumb" rabies appear depressed, lethargic, and uncoordinated. Gradually they become completely paralyzed. When their throat and jaw muscles are paralyzed, the animals will drool and have difficulty swallowing.

Rabies causes about 55,000 human deaths annually worldwide, with 95% of human deaths occurring in Asia and Africa. Roughly 97% of human rabies cases result from dog bites. In the U.S., animal control and vaccination programs have effectively eliminated domestic dogs as reservoirs of rabies. In several countries, including Australia and Japan, rabies carried by terrestrial animals has been eliminated entirely. While rabies was once eradicated in the United Kingdom, infected bats have recently been found in Scotland. In the U.S., the widespread vaccination of domestic dogs and cats and the development of effective human vaccines and immunoglobulin treatments has dropped the number of recorded human deaths from 100 or more annually in the early 20th century, to one to two per year (mostly caused by bat bites). Modern cell-based vaccines are similar to flu shots in terms of pain and side effects. The old nerve-tissue-based vaccinations that require multiple painful injections into the abdomen with a large needle are cheap, but are being phased out and replaced by affordable World Health Organization intradermal vaccination regimens.

Rabies may be diagnosed by PCR or viral culture of brain samples after death, or from skin samples taken before. Diagnosis can be made from saliva, urine, and cerebrospinal fluid samples with less accuracy. Cheaper rabies diagnosis will become possible for low-income settings using basic light microscopy techniques.

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15.5B: Poliomyelitis

Poliomyelitis is an infection by the polio virus that affects the motor neurons of the central nervous system.

Learning Objectives

- Describe poliomyelitis and its effect on motor neurons

Key Points

- Spinal polio is the most common type of polio and results in asymmetric paralysis, usually involving the legs.
- Bulbar polio is infection of the cranial nerves and causes weakness and paralysis in muscles innervated by the cranial nerves, while bulbospinal polio occurs when both the cranial nerves and spinal nerves are affected.
- Although approximately 90% of polio infections cause no symptoms at all, affected individuals can exhibit a range of symptoms if the virus enters the blood stream.

Key Terms

- **motor neuron**: A neuron located in the central nervous system that projects its axon outside the CNS and directly or indirectly control muscles.
- **spinal polio**: Spinal polio is characterized by asymmetric paralysis that most often involves the legs.
- **poliomyelitis**: acute infection by the poliovirus, especially of the motor neurons in the spinal cord and brainstem, leading to muscle weakness, paralysis and sometimes deformity
- **paralysis**: The complete loss of voluntary control of part of person's body, such as one or more limbs.

OVERVIEW

Poliomyelitis, often called polio or infantile paralysis, is an acute, viral, infectious disease spread from person to person, primarily via the fecal-oral route.

Although approximately 90% of polio infections cause no symptoms at all, affected individuals can exhibit a range of symptoms if the virus enters the blood stream. In about 1% of cases, the virus enters the central nervous system, preferentially infecting and destroying motor neurons, leading to muscle weakness and acute flaccid paralysis.

Different types of paralysis may occur, depending on the nerves involved. Spinal polio is the most common form, characterized by asymmetric paralysis that most often involves the legs. Bulbar polio leads to weakness of muscles innervated by cranial nerves. Bulbospinal polio is a combination of bulbar and spinal paralysis.



Figure: **Polio**: Man on street with atrophy and paralysis of the right leg and foot due to polio.

BACKGROUND

Poliomyelitis was first recognized as a distinct condition by Jakob Heine in 1840. Its causative agent, poliovirus, was identified in 1908 by Karl Landsteiner. Although major polio epidemics were unknown before the late 19th century, polio was one of the most dreaded childhood diseases of the 20th century. Polio epidemics have crippled thousands of people, mostly young children; the disease has caused paralysis and death for much of human history.

Polio had existed for thousands of years quietly as an endemic pathogen until the 1880s, when major epidemics began to occur in Europe; soon after, widespread epidemics appeared in the United States. By 1910, much of the world experienced a dramatic increase in polio cases and epidemics became regular events, primarily in cities during the summer months. These epidemics—which left thousands of children and adults paralyzed—provided the impetus for a "Great Race" towards the development of a vaccine.

DEVELOPMENT OF A VACCINE

Developed in the 1950s, polio vaccines are credited with reducing the global number of polio cases per year from many hundreds of thousands to today under a thousand. Enhanced vaccination efforts led by the World Health Organization, UNICEF, and Rotary International could result in global eradication of the disease.

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15.5C: Hantavirus

Hantaviruses are negative-sense RNA viruses that sometimes lead to hemorrhagic fever with renal syndrome in humans.

Learning Objectives

- Paraphrase the causes of hantavirus and the phases of symptoms: febrile, hypotensive, oliguric, diuretic and convalescent

Key Points

- The name hantavirus comes from the Hantaan River area in South Korea, where the first known strain – Hantaan virus (HTNV) – was isolated in 1978.
- Human infections of hantaviruses have almost entirely been linked to human contact with rodent excrement, thus, rodent control is the primary strategy for preventing hantavirus infection.
- There is no known antiviral treatment, but natural recovery from the virus is possible.

Key Terms

- **hypoxemia**: an abnormal deficiency in the concentration of oxygen in the blood, be it the partial pressure of oxygen (mm Hg), the content of oxygen (ml oxygen per dl of blood) or the percent saturation of the blood's hemoglobin, singly or in combination.
- **tachycardia**: a rapid resting heart rate, especially one above 100 beats per minute.
- **proteinuria**: excessive protein in the urine.

Hantaviruses are negative sense RNA viruses and are a relatively newly discovered genus in the Bunyaviridae family. The name hantavirus comes from the Hantaan River area in South Korea, where the first known strain – Hantaan virus (HTNV) – was isolated in 1978. Although some hantaviruses lead to potentially fatal diseases, such as hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), not all are associated with human disease.

Human infections of hantaviruses have almost entirely been linked to human contact with rodent excrement, thus, rodent control is the primary strategy for preventing hantavirus infection. Human-to-human transmission (via urine, saliva, etc.) may also occur, and has been recently reported with the Andes virus in South America.

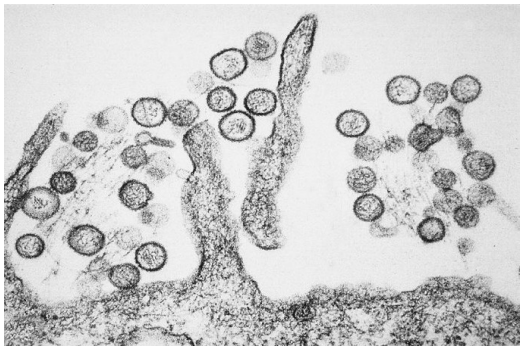

Figure: **Hantavirus pulmonary syndrome**: Hantaviruses that cause Hantavirus pulmonary syndrome (HPS) are carried in rodent droppings, especially the deer mouse. Incubation lasts for 1–5wks. Sickness begins with fever and muscle aches, followed by shortness of breath and coughing.

HTNV is one of several hantaviruses that cause hemorrhagic fever with renal syndrome (HFRS), formerly known as Korean hemorrhagic fever. HFRS has an incubation time of two to four weeks in humans before symptoms of infection occur. The symptoms of HFRS can be split into five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. The febrile phase begins two to three weeks after exposure, and normally lasts from three to seven days. Symptoms include fever, chills, diarrhea, malaise, headaches, nausea, abdominal and back pain, and respiratory and gastro-intestinal problems. These symptoms can resemble that of the flu. The hypotensive phase occurs when the blood platelet levels drop, and can lead to tachycardia and hypoxemia. This phase can last for 2 days. The oliguric phase begins with renal failure and proteinuria, and lasts from three to seven days. The diuretic phase is characterized by excessive urination (diuresis) of up to six liters per day, and can last for a couple of days up to a week. Although there is no known antiviral treatment for hantavirus, natural recovery is possible. The phase where symptoms begin to improve is the convalescent phase.

Hantavirus pulmonary syndrome (HPS) is another potentially fatal disease caused by hantavirus infection. Although rare, HPS is fatal in up to 60% of cases. HPS has been identified throughout the United States, and was first recognized in 1993 in the southwest where it was originally referred to as the “Four Corners disease. ” The symptoms are very similar to those of HFRS. Additionally, patients will develop difficulty breathing, coughing and shortness of breath, and may lead to cardiovascular shock.

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15.5D: Arboviral Encephalitis

Arboviral encephalitis (acute swelling in the brain) is caused by a group of arthropod-transmitted viruses.

Learning Objectives

- Examine the mode of transmission and causes of arboviral encephalitis

Key Points

- Arthropod vectors transmit the virus upon biting, allowing the virus to enter the circulatory system and replicate.
- Arboviral encephalitis are found in many places throughout the world, and include California encephalitis, Japanese encephalitis, St. Louis encephalitis, Tick-borne encephalitis, and West Nile fever.
- TBE Infection can be reliably prevented by vaccination, but is incurable once manifested.

Key Terms

- **sequelae**: A pathological condition resulting from a disease, injury, or other trauma.
- **encephalitis**: an inflammation of the brain
- **viremia**: A medical condition where viruses enter the bloodstream and hence have access to the rest of the body.
- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.

Arboviral encephalitis are a group of arthropod-transmitted viruses that cause encephalitis (acute swelling in the brain). The word “arbovirus” directly refers to an ARthropod-BOrne virus. Arthropod vectors transmit the virus upon biting, allowing the virus to enter the circulatory system and replicate and shed additional infection into the bloodstream (viremia).

The majority of the arboviruses are spherical in shape although a few are rod-shaped. They are 17-150 nm in diameter and most have an RNA genome (the single exception is African swine fever virus, which has a DNA genome). Many arboviruses (such as African Swine Fever virus) do not infect humans or cause only mild and transient infections characterized by fever, headache, and rash. Those of the arboviral encephalitis group, however, can cause epidemic disease and severe infections that can be fatal. Arboviral encephalitis are found in many places throughout the world, and include California encephalitis, Japanese encephalitis, St. Louis encephalitis, Tick-borne encephalitis, and West Nile fever.

Tick-borne encephalitis (TBE) is an infectious disease of the central nervous system. It can infect a range of hosts including ruminants, birds, rodents, carnivores, horses, and humans. The disease can be zoonotic, with ruminants and dogs providing the principal source of infection for humans. TBE is transmitted through the bite of several species of infected ticks, including *Ixodes scapularis*, *Ixodes ricinus*and *Ixodes persulcatus*, and manifests most often as meningitis, encephalitis, or meningoencephalitis.



Figure: **Chelicera of the sheep tick**: Sheep ticks (Ixodes ricinus) such as this engorged female transmit encephalitis.

TBE Infection can be reliably prevented by vaccination, but is incurable once manifested. Long-lasting or permanent neuropsychiatric sequelae are observed in 10-20% of infected patients; morality occurs in only 1-2% of the infected, with deaths occurring 5 to 7 days after the onset of neurologic symptoms.

TBE and other arboviral encephalitis can be diagnosed through a combination of blood tests, particularly immunologic, serologic, and/or virologic techniques such as ELISA, complement fixation, polymerase chain reaction, Neutralization test, and Hemoagglutination Inhibition test.

Because the arboviral encephalitides are viral diseases, antibiotics are not effective for treatment and no effective antiviral drugs have been discovered yet. Treatment is therefore only supportive, attempting to deal with problems such as swelling of the brain, loss of the automatic breathing, activity of the brain, and other treatable complications like bacterial pneumonia.

Therefore, the immune system plays an important role in defense against arbovirus infections. Arboviruses usually stimulate the production of interferons and antibodies, which help to diminish the extent of viremia. Cell-mediated immunity is also important. Increased immunity is observed with age progression.

Vector control measures, such as habitat control (including the elimination of stagnant water and the spraying of insecticides), are essential to reducing the transmission of disease by arboviruses. People can also reduce the risk of getting bitten by arthropods by employing personal protective measures such as sleeping under mosquito nets, wearing protective clothing, applying insect repellents, tick-checks, and avoiding areas known to harbor high arthropod populations.

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15.5E: Rickettsial Diseases

Rickettsia is a genus of bacteria that can be transmitted by arthropod vectors to humans, causing diseases.

Learning Objectives

- List the characteristics of Rickettsia species

Key Points

- Rickettsia are obligate intracellular parasites, and must replicate within the cytoplasm of eukaryotic host cells.
- Rickettsia species are carried by many ticks, fleas, and lice, and cause diseases in humans such as typhus, rickettsialpox, Boutonneuse fever, African tick bite fever, Rocky Mountain spotted fever, Flinders Island spotted fever, and Queensland tick typhus (Australian Tick Typhus).
- Rickettsia are one of closest living relatives to bacteria that were the origin of the mitochondria organelle that exists inside most eukaryotic cells. Indeed, certain segments of Rickettsia genomes resemble that of mitochondria, and ATP production is the same as that in mitochondria.

Key Terms

- **parthenogenesis**: a form of asexual reproduction in which growth and development of embryos occurs without fertilization.
- **pleomorphic**: the ability to alter shape or size in response to environmental conditions.

Rickettsia is a genus of bacteria that can be transmitted by arthropod vectors to humans, causing disease. Rickettsia species are non-motile, Gram-negative, non-sporeforming, highly pleomorphic bacteria that can present as cocci (0.1 μm in diameter), rods (1–4 μm long), or thread-like (10 μm long). They are obligate intracellular parasites, and must replicate within the cytoplasm of eukaryotic host cells. Rickettsia are one of closest living relatives to bacteria that were the origin of the mitochondria organelle that exists inside most eukaryotic cells. Unlike viruses, Rickettsia possess true cell walls and are similar to other gram-negative bacteria. Despite a similar name, Rickettsia bacteria do not cause rickets, which is a result of vitamin D deficiency.

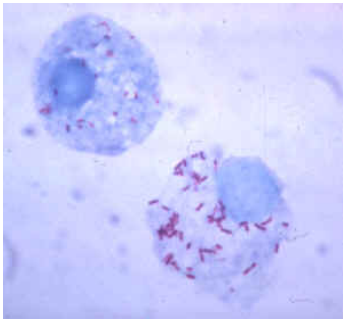

Figure: **A Microbe versus Animal Cell**: The large spheres are tick cells. The purple bars and dots are the bacterium Rickettsia rickettsii, which is the causative agent of Rocky Mountain spotted fever. Rickettsia rickettsii is a small bacterium that grows inside the cells of its hosts. These bacteria range in size from 0.2 x 0.5 micrometers to 0.3 x 2.0 micrometers.

Rickettsia species are carried by many ticks, fleas, and lice, and cause diseases in humans such as typhus, rickettsialpox, Boutonneuse fever, African tick bite fever, Rocky Mountain spotted fever, Flinders Island spotted fever, and Queensland tick typhus (Australian Tick Typhus). They have also been associated with a range of plant diseases.

Rickettsia can be classified into three groups based on serology and DNA sequencing: spotted fever, typhus, and scrub typhus. All three of these groups contain human pathogens. Recent studies reclassify the scrub typhus group as a new genus – Orienta, and suggest that the spotted fever group should be divided into two clades. Rickettsia are widespread, and can be associated with arthropods, leeches, and protists. Rickettsia found in Arthropods are generally associated with reproductive manipulation (such as parthenogenesis) to persist in host lineage.

Unlike free-living bacteria, Rickettsia species contain no genes for anaerobic glycolysis or those involved in the biosynthesis and regulation of amino acids and nucleosides. In this regard, certain segments of Rickettsia genomes resemble that of mitochondria, and ATP production is the same as that in mitochondria. (With the exception of *R. prowazekii*, whose genome contains a complete set of genes encoding for the tricarboxylic acid cycle and the respiratory chain complex). The genomes of both Rickettsia and mitochondria are frequently said to be “small, highly derived products of several types of reductive evolution. ”

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15.5F: Lyme Disease

Lyme disease is caused by bacteria from the Borrelia genus.

Learning Objectives

- Discuss the mode of transmission and symptoms for lyme disease

Key Points

- Borrelia is transmitted to humans through the bite of infected ticks belonging to a few species of the genus Ixodes ("hard ticks").
- Lyme disease can affect multiple body systems and produce a range of symptoms.
- Lyme disease begins with a characterized bullseye rash called erythema chronicum migrans.

Key Terms

- **nymphal**: In some invertebrates, of or pertaining to the immature form.
- **asymptomatic**: not exhibiting any symptoms of disease.
- **paraplegia**: A condition where the lower half of a patient's body is paralyzed and cannot move.

Lyme disease (aka Lyme borreliosis) is caused by bacteria from the Borrelia genus, and is the most common tick-borne disease in the Northern Hemisphere. *Borrelia burgdorferi sensu stricto* is the main cause of Lyme disease in North America, whereas *Borrelia afzelii* and *Borrelia garinii* cause most European cases. Borrelia is transmitted to humans through the bite of infected ticks belonging to a few species of the genus Ixodes ("hard ticks"). The disease is named after the towns of Lyme and Old Lyme, Connecticut, where a number of cases were identified in 1975. Although it was realized that Lyme disease was a tick-borne disease in 1978, the cause of the disease remained a mystery until 1981, when *B. burgdorferi* was identified.



Figure: **Deer Tick**: Nymphal and adult deer ticks can be carriers of Lyme disease. Nymphs are about the size of a poppy seed.

Lyme disease can affect multiple body systems and produce a range of symptoms, though not all patients with Lyme disease will have all symptoms, and many of the symptoms are not specific to Lyme disease. The incubation period from infection to the onset of symptoms is usually one to two weeks, but can be much shorter (days), or much longer (months to years). Most infections are caused by ticks in the nymphal stage, as they are very small and may feed undetected for long periods of time, with symptoms occurring most often from May through September because of this life cycle. An infected tick must be attached for at least a day for transmission to occur, and only about 1% of recognized tick bites result in Lyme disease.

Lyme disease begins with a localized infection, affecting the area at the site of the tick bite with a circular, outwardly expanding rash called erythema chronicum migrans (EM), which gives the appearance of a bullseye. Patients may also experience flu-like symptoms, such as headache, muscle soreness, fever, malaise, fatigue, and depression. In most cases, the infection and its symptoms are eliminated by antibiotics, especially if the illness is treated early. Delayed or inadequate treatment can lead to more serious symptoms, which can be disabling and difficult to treat. Asymptomatic infections may occur, though this is the case in less than 7% of infected individuals in the United States. Asymptomatic infection may be more common in Europe.



Figure: **Lyme Disease**: Erythematous rash in the pattern of a “bull’s-eye” from Lyme disease.

Left untreated, Borrelia bacteria begins to spread through the bloodstream within days to weeks after the onset of local infection, progressing symptoms to the joints, heart, and central nervous system. These symptoms include migrating pain in muscles, joints, and tendons; neck stiffness; sensitivity to light; and heart palpitations and dizziness caused by changes in heartbeat. Acute neurological problems, termed “neuroborreliosis”, appear in 10–15% of untreated patients. EM may even develop at sites across the body that bear no relation to the original tick bite. Radiculoneuritis causes shooting pains that may interfere with sleep, as well as abnormal skin sensations. Mild encephalitis may lead to memory loss, sleep disturbances, or mood changes.

After several months, untreated or inadequately treated patients may go on to develop severe and chronic symptoms, including permanent paraplegia in the most extreme cases. Patients may develop Lyme arthritis, usually affecting the knees; nerve pain radiating out of the spine (Bannwarth syndrome); and shooting pains, numbness, and tingling in the hands or feet. A neurologic syndrome called Lyme encephalopathy is associated with subtle cognitive problems, such as difficulties with concentration and short-term memory. These patients may experience profound fatigue. Chronic encephalomyelitis can involve cognitive impairment, weakness in the legs, awkward gait, facial palsy, bladder problems, vertigo, and back pain. In rare cases, untreated Lyme disease may cause frank psychosis, which has been mis-diagnosed as schizophrenia or bipolar disorder. Panic attacks and anxiety can occur; as well as delusional behavior and detachment from themselves and reality.

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15.5G: West Nile Virus

West Nile virus is a mosquito-borne arbovirus found in temperate and tropical regions of the world.

Learning Objectives

- Discuss the causes, symptoms and diseases (West Nile encephalitis, meningitis, meningoencephalitis and poliomyelitis) caused by the West Nile virus (WNV)

Key Points

- WNV is considered to be an endemic pathogen in Africa, Asia, Australia, the Middle East, Europe and in the United States, with one of the worst epidemics occurring in 2012.
- Birds are the most commonly infected animal, and serve as the prime reservoir host.
- The specific neurological diseases which may occur are encephalitis, meningitis, meningoencephalitis, and poliomyelitis.

Key Terms

- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.

West Nile virus (WNV) is a mosquito-borne zoonotic arbovirus belonging to the genus Flavivirus, and is found in temperate and tropical regions of the world.

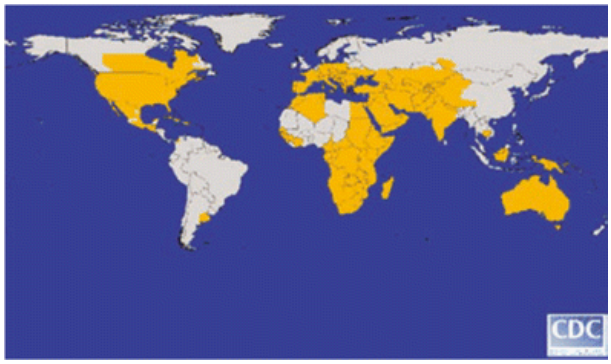

Figure: **Global distribution of West Nile virus**: Global distribution of West Nile virus.

WNV was first identified in the West Nile subregion in the East African nation of Uganda in 1937. Prior to the mid 1990s, WNV disease occurred only sporadically and was considered a minor risk for humans. This was until an outbreak in Algeria in 1994, with cases of WNV-caused encephalitis, and the first large outbreak in Romania in 1996, with a high number of cases with neuroinvasive disease. WNV has now spread globally, with the first case in the Western Hemisphere being identified in New York City in 1999. The virus has now spread across the continental United States, north into Canada, and southward into the Caribbean Islands and Latin America. The US experienced one of its worst epidemics to date in 2012. WNV also spread to Europe, beyond the Mediterranean Basin, with a new strain of the virus recently identified in Italy (2012). WNV is now considered to be an endemic pathogen in Africa, Asia, Australia, the Middle East, Europe and in the United States.

The main mode of WNV transmission is by mosquitoes, the prime vector. WNV has been found in various species of ticks. However, current research suggests they are not important vectors of the virus. WNV infects various mammal species, including humans. It has also been identified in reptilians (including alligators and crocodiles) and amphibians. Birds, especially passerines, are the most commonly infected animal, and serve as the prime reservoir host. Many species – including humans – do not develop viral levels sufficient to transmit the disease to uninfected mosquitoes, and are thus not considered major factors in WNV transmission.



Figure: **Transmission of the West Nile virus**: The proboscis of a female mosquito pierces the epidermis and dermis to allow it to feed on humanblood from a capillary: this one is almost fully engorged. The mosquito injects saliva which contains an anesthetic, and an anticoagulant into the puncture wound; and in infected mosquitoes, the West Nile virus.

Approximately 80% of West Nile virus infections in humans cause no symptoms. West Nile fever is the manifestation of symptoms, with an incubation period typically between 2 and 15 days. Symptoms may include fever, headaches, fatigue, muscle pain or aches, malaise, nausea, anorexia, vomiting, myalgias and rash. Less than 1% of the cases are severe and result in neurological disease when the central nervous system is affected. People of advanced age, the very young, or those with immunosuppression are most susceptible.

The specific neurological diseases which may occur are:

- West Nile encephalitis, which causes inflammation of the brain
- West Nile meningitis, which causes inflammation of the meninges (the protective membranes that cover the brain and spinal cord)
- West Nile meningoencephalitis, which causes inflammation of the brain and surrounding meninges
- West Nile poliomyelitis (spinal cord inflammation, which results in a syndrome similar to polio that may cause acute flaccid paralysis).

Currently, no vaccine against WNV infection is available. The best method to reduce the rates of WNV infection is by public mosquito control (particularly the elimination of standing water) and by personal protection (mosquito nets and repellent).

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15.5H: Plague

The plague is an infectious disease caused by the Gram-negative rod-shaped bacteria *Yersinia pestis*.

Learning Objectives

- Outline the route of pathogenesis for Yersinia pestis

Key Points

- Although bubonic plague is often used synonymously with plague, it refers specifically to an infection that enters through the skin and travels through the lymph nodes (buboes).
- Septicemic plague is a deadly blood infection; symptoms include hypotension, hepatosplenomegaly, delirium, seizures in children, shock, lethargy, and fever. Pneumonic plague manifests as a severe lung infection.
- Y. pestis is spread most commonly between rodents (both urban and wild) and fleas.

Key Terms

- **pneumonic plague**: a severe type of lung infection, one of three main forms of plague, all of which are caused by the bacterium Yersinia pestis
- **bubonic plague**: a contagious, often fatal, epidemic disease caused by the bacterium Yersinia pestis, transmitted by the bite of fleas from an infected person or rodent, especially a rat, and characterized by delirium, chills, fever, vomiting, diarrhea, and the formation of buboes
- **hepatosplenomegaly**: enlargement of both the liver and spleen.
- **plague**: an epidemic or pandemic caused by any pestilence, but specifically by the above disease

The plague is an infectious disease caused by the Gram-negative rod-shaped bacteria *Yersinia pestis* . Human *Y. pestis* infection is manifested in three main forms: pneumonic, septicemic, and the notorious bubonic plagues. All three forms are widely believed to have been responsible for a number of high-mortality epidemics throughout human history, including the Plague of Justinian in 542, and the Black Death that accounted for the death of at least one-third of the European population between 1347 and 1353. It has now been conclusively shown that these plagues originated in rodent populations in China. Thousands of cases of the plague are still reported every year; with proper treatment, the prognosis for victims is now much improved. The plague also has a detrimental effect on non-human mammals. In the United States, animals such as the black-tailed prairie dog and the endangered black-footed ferret are under threat from the disease.

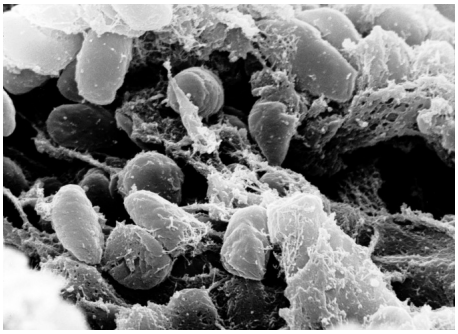

Figure: **Yersinia pestis**: Scanning electron micrograph depicting a mass of Yersinia pestis bacteria (the cause of bubonic plague) in the foregut of the flea vector.

Although bubonic plague is often used synonymously with plague, it refers specifically to an infection that enters through the skin and travels through the lymph nodes (buboes). The incubation period of bubonic plague is from 2-6 days, while the bacteria actively replicate. Symptoms include a lack of energy, fever, headache and chills, and swelling of lymph nodes resulting in buboes, the classic sign of bubonic plague. Septicemic plague is a deadly blood infection; symptoms include hypotension, hepatosplenomegaly, delirium, seizures in children, shock, lethargy, and fever. Pneumonic plague manifests as a severe lung infection, and is more virulent and rare than bubonic plague. Symptoms include fever, chills, coughing, chest pain, dyspnea, hemoptysis, lethargy, hypotension, and shock. Symptoms of the plague are not always present, or the patient may die before any symptoms appear.

Y. pestis is spread most commonly between rodents (both urban and wild) and fleas. Any infected animal can transmit the infection to humans through contact with skin tissue. Humans can also spread the bacteria to other humans through sneezing, coughing, or with direct contact with infected tissue. The reservoir commonly associated with *Y. pestis* is several species of rodents. In the steppes, the reservoir species is believed to be principally the marmot. In the United States, several species of rodents are thought to maintain *Y. pestis*. However, the expected disease dynamics have not been found in any rodent species. It is known that rodent populations will have a variable resistance, which could lead to a carrier status in some individuals. In some regions of the world, the reservoir of infection is not clearly identified, which complicates prevention and early warning programs.

The transmission of *Y. pestis* by fleas is well characterized. Initial acquisition of *Y. pestis* by the vector occurs during feeding on an infected animal. Several proteins then contribute to the maintenance of the bacteria in the flea digestive tract, among them the hemin storage (Hms) system and Yersinia murine toxin (Ymt). Although Yersinia murine toxin is highly toxic to rodents and was once thought to be produced to ensure reinfection of new hosts, it has been demonstrated that Ymt is important for the survival of *Y. pestis* in fleas. The Hms system plays an important role in the transmission of *Y. pestis* back to a mammalian host. While in the insect vector, proteins encoded by Hms genetic loci induce biofilm formation in the proventriculus, a valve connecting the midgut to the esophagus. Aggregation in the biofilm inhibits feeding, as a mass of clotted blood and bacteria forms (referred to as “Bacot’s block”). Transmission of *Y. pestis* occurs during the futile attempts of the flea to feed. Ingested blood is pumped into the esophagus, where it dislodges bacteria lodged in the proventriculus and is regurgitated back into the host circulatory system.



Figure: **A flea infected with yersinia pestis**: A flea infected with yersinia pestis, shown as a dark mass. The foregut of this flea is blocked by a Y. pestis biofilm, which is a prerequisite for efficient transmission.

The pathogenesis of *Y. pestis* infection in mammalian hosts is due to several factors. The bacteria proliferates inside lymph nodes where it is able to avoid destruction by cells of the immune system such as macrophages. *Y. pestis* is able to suppress the immune system, avoiding normal immune system responses such as phagocytosis and antibody production. Flea bites allow for the bacteria to pass the skin barrier. *Y. pestis* expresses the yadBC gene, which is similar to adhesins in other Yersinia species, allowing for adherence and invasion of epithelial cells. Finally, *Y. pestis* expresses a plasminogen activator that is an important virulence factor for pneumonic plague, which may also degrade on blood clots in order to facilitate systematic invasion. Two important anti-phagocytic antigens, Fraction 1 (F1) and LcrV (V), are both important for virulence. Natural or induced immunity is achieved, therefore, by the production of specific opsonic antibodies against F1 and V antigens.

The traditional first line treatment for *Y. pestis* has been the antibiotics streptomycin, chloramphenicol, tetracycline, and fluoroquinolones. Antibiotic treatment alone is insufficient for some patients, who may also require circulatory, ventilator, or renal support.

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SECTION OVERVIEW

15.6: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System

Topic hierarchy

15.6A: Cryptococcosis

15.6B: African Trypanosomiasis

15.6C: Amoebic Meningoencephalitis

15.6D: Bovine Spongiform Encephalopathy

15.6E: Variant Creutzfeldt-Jakob Disease

15.6F: Chronic Fatigue Syndrome

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15.6A: Cryptococcosis

Cryptococcosis is a disease caused by fungi that can be fatal.

Learning Objectives

- Recognize the causes and symptoms associated with cryptococcosis

Key Points

- Cryptococcal meningitis is caused when the disease-causing fungus gets in the membranes around the brain.
- Cryptococcosis is an opportunistic infection, it often affects people who are immune -compromised, such as people who have AIDS.
- As people who get cryptoccosis often have other health problems, even treatment with anti- fungal agents may not cure the infection.
- Cryptococcosis can infect animals such as cats; it is not solely a human pathogen.

Key Terms

- **meninges**: The three membranes that envelop the brain and spinal cord.
- **propagule**: A reproductive particle released by an organism that may germinate into another.

Cryptococcosis, or cryptococcal disease, is a potentially fatal fungal disease. It is caused by one of two species: Cryptococcus neoformans and Cryptococcus gattii. These were all previously thought to be subspecies of C. neoformans, but have now been identified as distinct species. Cryptococcosis is believed to be acquired by inhalation of the infectious propagule from the environment. Although the exact nature of the infectious propagule is unknown, the leading hypothesis is the basidiospore created through sexual or asexual reproduction.

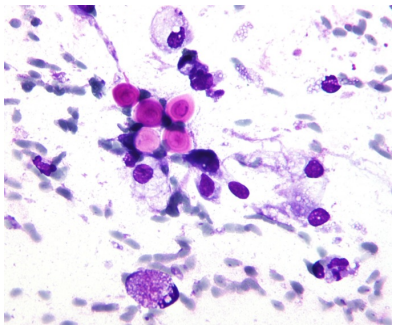

Figure: **Cryptococcus**: A micrograph of cryptococcus (purple), the fungus that can cause cryptococcosis.

Causes

Cryptococcal meningitis (infection of the meninges, the tissue covering the brain) is believed to result from dissemination of the fungus from either an observed or unappreciated pulmonary infection. Often there is also silent dissemination throughout the brain when meningitis is present. Cryptococcus gattii causes infections in immunocompetent people (those having a functioning immune system), but C. neoformans v. grubii, and v. neoformans usually only cause clinically evident infections in persons who have some form of defect in their immune systems (immunocompromised persons). People who have defects in their cell-mediated immunity; for example, people with AIDS; are especially susceptible to disseminated cryptococcosis. Cryptococcosis is often fatal, even if treated. The ten-week survival averages near 70% with optimal therapy.

Although the most common presentation of cryptococcosis is of C. neoformans infection in an immunocompromised person (such as persons living with AIDS), the C. gattii is being increasingly recognised as a pathogen in presumptively immunocompetent hosts, especially in Canada and Australia. This may be due to rare exposure and high pathogenicity, or to unrecognised isolated defects in immunity, specific for this organism.

Cryptococcosis is a defining opportunistic infection for AIDS. Other conditions which pose an increased risk include certain lymphomas (e.g. Hodgkin's lymphoma), sarcoidosis, liver cirrhosis, and patients on long-term corticosteroid therapy. Distribution is worldwide in soil. The prevalence of cryptococcosis has been increasing over the past 20 years for many reasons, including the increase in incidence of AIDS and the expanded use of immunosuppressive drugs.

Treatment

Treatment options in non-AIDS patients who have reduced immune-system function is not well studied. Intravenous Amphotericin B combined with oral flucytosine may be effective. Every attempt should be made to reduce the amount of immunosuppressive medication until the infection is resolved. Persons living with AIDS often have a greater chance of disease and higher mortality (30-70% at ten-weeks), but recommended therapy is with antifungal agents such as Amphotericin B and flucytosine.

Cryptococcosis in Animals

Cryptococcosis is also seen in cats and occasionally dogs. It is the most common deep fungal disease in cats, usually leading to chronic infection of the nose and sinuses, and skin ulcers. Cats may develop a bump over the bridge of the nose from local tissue inflammation. It can be associated with feline leukemia virus infection in cats. Cryptococcosis is most common in dogs and cats, but cattle, sheep, goats, horses, wild animals and birds can also be infected. Soil, fowl manure, and pigeon droppings are among the sources of infection.

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15.6B: African Trypanosomiasis

Sleeping sickness is caused by a protozoa transmitted by the tsetse fly.

Learning Objectives

- Outline the life cycle of Trypanosoma brucei and its route of transmission that causes African trypanosomiasis

Key Points

- The disease is caused by protozoa of the species Trypanosoma brucei, which in a mammalian blood system become a trypomastigote and travels throughout the host mammalian and infects spinal fluid and lymph nodes.
- The protozoa Trypanosoma brucei infects the tsetse fly when it feeds on the blood of an infected mammal. Once infected a tsetse fly can transmit the disease to other mammals.
- Initially, sleeping sickness has many symptoms of other viral infections, but if left untreated it will affect the nervous system, causing lethargy.

Key Terms

- **trypomastigote**: A stage in unicellular life-cycle, typically trypanosomes, where the flagellum is posterior of the nucleus, and connected to the cell body by a long undulating membrane.
- **epimastigotes**: A stage in unicellular life-cycle, typically trypanosomes, where the flagellum is anterior of the nucleus, and attached the cell body by a short membrane.

Human African trypanosomiasis, sleeping sickness, African lethargy, or Congo trypanosomiasis is a parasitic disease of people and animals, caused by protozoa of the species Trypanosoma brucei and transmitted by the tsetse fly. The disease is endemic in some regions of sub-Saharan Africa, covering areas in about 37 countries containing more than 60 million people. An estimated 50-70 thousand people are currently infected, the number having declined somewhat in recent years. The number of reported cases was below ten thousand in 2009, the first time in 50 years. Many cases are believed to go unreported. About 48 thousand people died of it in 2008. Four major epidemics have occurred in recent history: one from 1896-1906, primarily in Uganda and the Congo Basin, two epidemics in 1920 and 1970 in several African countries, and a recent 2008 epidemic in Uganda.

Transmission

The tsetse fly (genus Glossina) is a large, brown, biting fly that serves as both a host and vector for the trypanosome parasites. While taking blood from a mammalian host, an infected tsetse fly injects metacyclic trypomastigotes into skin tissue. From the bite, parasites first enter the lymphatic system and then pass into the bloodstream. Inside the mammalian host, they transform into bloodstream trypomastigotes, and are carried to other sites throughout the body, reach other body fluids (e.g., lymph, spinal fluid), and continue to replicate by binary fission. The entire life cycle of African trypanosomes is represented by extracellular stages. A tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host. In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission, leave the midgut, and transform into epimastigotes. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission.The entire life cycle of the fly takes about three weeks.

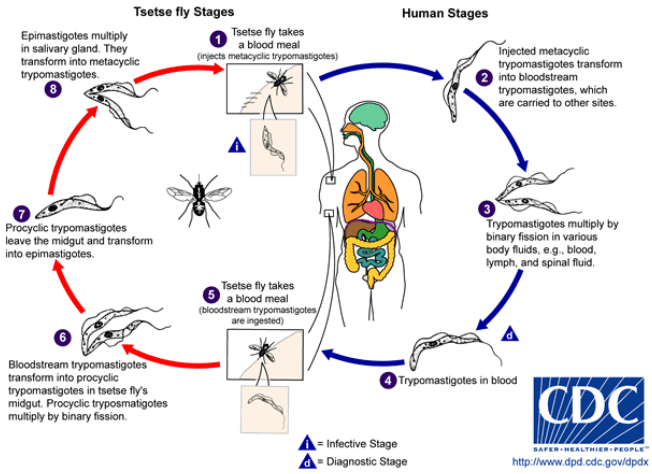

Figure: **Life Cycle of the Trypanosoma brucei parasite**: Here is an outline of the life cycle of the protozoa Trypanosoma brucei, the parasite responsible for African trypanosomiasis (sleeping sickness).

In addition to the bite of the tsetse fly, the disease can be transmitted by, mother-to-child infection; the trypanosome can sometimes cross the placenta and infect the fetus. Transmission can also occur in laboratories by accidental infections; for example, through the handling of blood of an infected person and organ transplantation, though this is uncommon. Blood transfusions and possibly sexual contact, are two other causes.

Symptoms

African trypanosomiasis symptoms occur in two stages. The first stage, known as the haemolymphatic phase, is characterized by fever, headaches, joint pains, and itching. Invasion of the circulatory and lymphatic systems by the parasites is associated with severe swelling of lymph nodes, often to tremendous sizes. If left untreated, the disease overcomes the host's defenses and can cause more extensive damage, broadening symptoms to include anemia, endocrine, cardiac, and kidney dysfunctions. The second phase, the neurological phase, begins when the parasite invades the central nervous system by passing through the blood–brain barrier. The term "sleeping sickness" comes from the symptoms of the neurological phase. The symptoms include confusion, reduced coordination, and disruption of the sleep cycle, with bouts of fatigue punctuated with manic periods, leading to daytime slumber and night-time insomnia. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma and death. Damage caused in the neurological phase is irreversible.

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15.6C: Amoebic Meningoencephalitis

Amoebic meningoencephalitis is an often-fatal central nervous system infection caused by Naegleria fowleri.

Learning Objectives

- Summarize the route of transmission and effects of infection by Naegleria fowleri

Key Points

- Amoebic meningoencephalitis is not actually caused by an ameoba but rather Naegleria fowleri a protist found in warm fresh water.
- Once Naegleria fowleri enters deep into the nasal passage, digesting through the olfactory bulbs it then migrates into the forebrain, where the protists eat neuronal tissue in the brain, leading to death within 14 days from initial exposure.
- The disease is largely asymptomatic until its final stages; often by the time it is diagnosed, it is too late to treat, causing a very high mortality rate.
- Antimicrobial drugs can combat Naegleria fowleri infection if it is treated soon enough. Avoiding the infection by wearing nose plugs when swimming in warm water is a good preventative measure.

Key Terms

- **anosmia**: Inability to smell; to perceive odors.
- **protist**: Any of the eukaryotic unicellular organisms including protozoans, slime molds and some algae; historically grouped into the kingdom Protoctista.
- **parosmia**: A distorted sense of smell, often resulting in phantom, non-existent, and mostly unpleasant, smells.
- **ageusia**: Partial or complete loss of the sense of taste.

Primary amoebic meningoencephalitis (PAM, or PAME) is a disease of the central nervous system caused by infection from *Naegleria fowleri*.

Naegleria fowleri is commonly referred to as an amoeba but is actually a unicellular parasitic protist that is ubiquitous in soils and warm, stagnant bodies of freshwater, especially during the summer months. Patients typically have a history of exposure to a natural body of water.

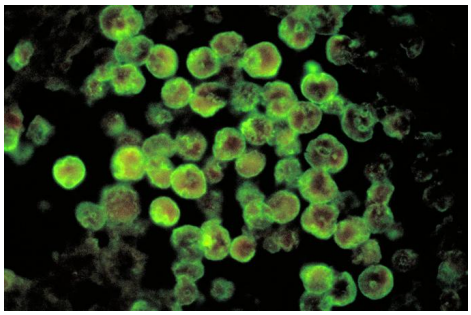

Figure: **Naegleria fowleri**: Antibody detection (green) of Naegleria fowleri, the organism responsible for Primary amoebic meningoencephalitis (PAM).

The organism specifically prefers temperatures above 32 °C, as might be found in a tropical climate or in water heated by geothermal activity. The organism is extremely sensitive to chlorine (<0.5 ppm). Exposure to the organism is extremely common due to its wide distribution in nature.

However, thus far the only route for Naegleria fowleri to enter the central nervous system is via deep insufflation of infected water as it attaches itself to the olfactory nerve, which is exposed only at the extreme vertical terminus of the paranasal sinuses.

When this occurs, it then migrates through the cribiform plate and into the olfactory bulbs of the forebrain, where it multiplies itself greatly by feeding on nerve tissue. During this stage, occurring approximately 3–7 days post-infection, the typical symptoms are parosmia, rapidly progressing to anosmia (with resultant ageusia) as the nerve cells of the olfactory bulbs are consumed and replaced with necrotic lesions.

After the organisms have multiplied and largely consumed the olfactory bulbs, the infection rapidly spreads through the mitral cell axons to the rest of the cerebrum, resulting in onset of frank encephalitic symptoms, including cephalgia (headache), nausea, and rigidity of the neck muscles, progressing to vomiting, delirium, seizures, and eventually irreversible coma. Death usually occurs within 14 days of exposure as a result of respiratory failure when the infection spreads to the brain stem, destroying the autonomic nerve cells of the medulla oblongata.

The disease is both exceptionally rare and highly lethal: there have been fewer than 200 confirmed cases in recorded medical history as of 2004, and 300 cases as of 2008, with an in-hospital case fatality rate of ~97% (3% patient survival rate). Its high mortality rate is largely blamed on the unusually non-suggestive symptomology in its early stages, compounded by the necessity of microbial culture of the cerebrospinal fluid to effect a positive diagnosis. The parasite also demonstrates a particularly rapid late-stage propagation through the nerves of the olfactory system to many parts of the brain simultaneously (including the vulnerable medulla).

Michael Beach, a recreational waterborne-illness specialist for the Centers for Disease Control and Prevention, stated in remarks to the Associated Press that the wearing of nose-clips to prevent nasal uptake of contaminated water would be an effective protection against contracting PAM, noting that, “You’d have to have water going way up in your nose to begin with”.

PAM can be effectively treated with antimicrobiotics, if the patient is treated early enough.

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15.6D: Bovine Spongiform Encephalopathy

Bovine spongiform encephalopathy (BSE) is a fatal neurodegenerative disease in cows.

Learning Objectives

- Recognize the route of transmission and causes of bovine spongiform encephalopathy (BSE)

Key Points

- BSE is probably caused by a misfolded protein known as a prion; a prion can cause other correctly folded proteins to misfold thus propagating the disease.
- Cooking of prions does not destroy them.
- Evidence exists that when the prions in cows that cause BSE are consumed by humans this causes prion transmission to humans and the neurodegenerative Creutzfeldt-Jakob disease.

Key Terms

- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **beta sheet**: A secondary structure in proteins consisting of multiple strands connected laterally.
- **alpha helix**: A secondary structure found in many proteins, where the amino acids are arranged in a coil, or helix, with almost no free space on the inside and all side chains being pointed towards the outside.

Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, is a fatal neurodegenerative disease in cattle that causes a spongy degeneration in the brain and spinal cord. BSE has a long incubation period, about 30 months to eight years, usually affecting adult cattle at a peak age of four to five years, all breeds being equally susceptible.



Figure: **Bovine spongiform encephalopathy (BSE)**: A cow suffering from BSE. The disease has progressed so far the animal cannot stand.

In the United Kingdom, the country worst affected, more than 180,000 cattle have been infected and 4.4 million slaughtered during the eradication program. The disease may be most easily transmitted to human beings by eating food contaminated with the brain, spinal cord or digestive tract of infected carcasses. However, it should also be noted that the infectious agent, although most highly concentrated in nervous tissue, can be found in virtually all tissues throughout the body, including blood. In humans, it is known as new variant Creutzfeldt–Jakob disease (vCJD or nvCJD), and by October 2009, had killed 166 people in the United Kingdom and 44 elsewhere. Between 460,000 and 482,000 BSE-infected animals had entered the human food chain before controls on high-risk offal were introduced in 1989.

The infectious agent in BSE is believed to be a specific type of misfolded protein called a prion. Prions will not disappear even if the beef containing them is cooked. Prion proteins carry the disease between individuals and cause deterioration of the brain.

BSE is a type of transmissible spongiform encephalopathy (TSE). TSEs can arise in animals that carry an allele which causes previously normal protein molecules to contort by themselves from an alpha helix arrangement to a beta sheet, which is the disease-causing shape for the particular protein. Transmission can occur when healthy animals come in contact with tainted tissues from others with the disease. In the brain, these proteins cause native cellular prion protein to deform into the infectious state,

which then goes on to deform further prion protein in an exponential cascade. This results in protein aggregates, which then form dense plaque fibers, leading to the microscopic appearance of “holes” in the brain, degeneration of physical and mental abilities, and ultimately death.

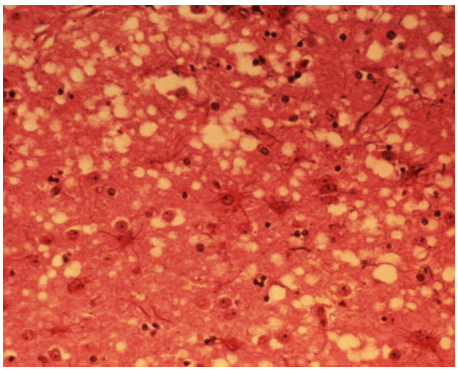

Figure: **BSE infected brain tissue**: This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic “holes” in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.

Different hypotheses exist for the origin of prion proteins in cattle. Two leading hypotheses suggest it may have jumped species from the disease scrapie in sheep, or that it evolved from a spontaneous form of “mad cow disease” that has been seen occasionally in cattle for many centuries. In the fifth century BC, Hippocrates described a similar illness in cattle and sheep, which he believed also occurred in man. Publius Flavius Vegetius Renatus recorded cases of a disease with similar characteristics in the fourth and fifth centuries. Recent research suggests mad cow disease is caused by a genetic mutation within a gene called the prion protein gene. The research shows, for the first time, that a 10-year-old cow from Alabama with an atypical form of bovine spongiform encephalopathy had the same type of prion protein gene mutation as found in human patients with the genetic form of Creutzfeldt–Jakob disease, also called genetic CJD, for short. Besides having a genetic origin, other human forms of prion diseases can be sporadic, as in sporadic CJD, as well as foodborne. They are contracted when people eat products contaminated with mad cow disease. This form of Creutzfeldt-Jakob disease is called variant CJD.

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15.6E: Variant Creutzfeldt-Jakob Disease

Variant Creutzfeldt–Jakob Disease (vCJD) is a fatal neurological disorder which is caused by prions.

Learning Objectives

- Generalize the role of prions in Creutsfeldt-Jakob disease

Key Points

- Bovine spongiform encephalopathy (BSE) is believed to be the cause of variant Creutzfeldt–Jakob (vCJD); BSE is a prion disease that affects cattle. In both humans and cattle the disease causes large holes in the brain.
- The prion the misfoled protein that causes vCJD has two conformations: one is the native form and is water soluble; the other is the disease form, which is water insoluble.
- The misfolded prion proteins can cause other normally folded pre-prion proteins to become prions, which disrupts the native proteins disrupting function leading to cell death.
- There is no known treatment for vCJD, except avoiding BSE contaminated meat.

Key Terms

- **Creutzfeldt–Jakob disease**: a rare, progressive, currently fatal disease of the nervous system, characterized by dementia and loss of muscle control; a prion disease, apparently transmissible from animals to humans by eating infected tissue, as well as from tissue interchanges among humans
- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **transmembrane**: traversing a cellular membrane

Creutzfeldt–Jakob disease, or CJD, is a degenerative neurological disorder (brain disease) that is incurable and invariably fatal. CJD is occasionally called a human form of mad cow disease (bovine spongiform encephalopathy or BSE), even though classic CJD is not related to BSE. However, given that BSE is believed to be the cause of variant Creutzfeldt–Jakob disease (vCJD) in humans, the two are often confused. In CJD, the brain tissue develops holes and takes on a sponge-like texture. This is due to a type of infectious protein called a prion. Prions are misfolded proteins which replicate by converting their properly folded counterparts.

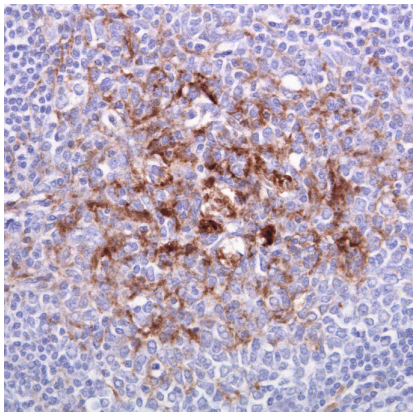

Figure: **A tonsil biopsy**: The brown staining is for the prion protein responsible for variant Creutzfeldt–Jakob disease prion.

Transmissible spongiform encephalopathy diseases are caused by prions. Thus, the diseases are sometimes called prion diseases. Other prion diseases include Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI) and Kuru in humans; as well as bovine spongiform encephalopathy (BSE, commonly known as mad cow disease) in cattle, chronic wasting disease (CWD) in elk and deer, and Scrapie in sheep. Alpers' syndrome in infants is also thought to be a transmissible spongiform encephalopathy caused by a prion.

The prion that is believed to cause Creutzfeldt–Jakob exhibits at least two stable conformations. One, the native state, is water-soluble and present in healthy cells. As of 2007, its biological function is presumably in transmembrane transport or signaling. The other conformational state is relatively water-insoluble and readily forms protein aggregates. People can also acquire CJD genetically through a mutation of the gene that codes for the prion protein (PRNP). This occurs in only 5–10% of all CJD cases.

The CJD prion is dangerous because it promotes refolding of native proteins into the diseased state. The number of misfolded protein molecules will increase exponentially and the process leads to a large quantity of insoluble protein in affected cells. This mass of misfolded proteins disrupts cell function and causes cell death. Mutations in the gene for the prion protein can cause a misfolding of the dominantly alpha helical regions into beta pleated sheets. This change in conformation disables the ability of the protein to undergo digestion. Once the prion is transmitted, the defective proteins invade the brain and are produced in a self-sustaining feedback loop.

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15.6F: Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is the most common persistent fatigue syndrome that affects people.

Learning Objectives

- Recognize the major symptoms associated with chronic fatigue syndrome

Key Points

- CFS is typified by extreme fatigue even in the absence of any type of exertion, and can affect people of all ages.
- There can be many non-fatigue symptoms associated with CFS, with many people exhibiting several different symptoms.
- While no direct association has been shown between a given virus and CFS, the onset of CFS is often preceded with viral infection type symptoms.

Key Terms

- **orthostatic**: Of, or relating to upright posture.
- **morbid**: Of, or relating to disease.
- **prevalence**: the total number of cases of a disease in the given statistical population at a given time, divided by the number of individuals in the population
- **encephalomyelitis**: Inflammation of the brain and spinal cord.

Chronic fatigue syndrome (CFS) is the most common name used to designate a significantly debilitating medical disorder or group of disorders. Generally defined by persistent fatigue accompanied by other specific symptoms for a minimum of six months in adults (and 3 months in children/adolescents), not due to ongoing exertion, not substantially relieved by rest, and not caused by other medical conditions. The disorder may also be referred to as myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS), chronic fatigue immune dysfunction syndrome (CFIDS), or several other terms.



Figure: **Chronic fatigue syndrome**: Sufferers of chronic fatigue syndrome experience tiredness and unrefreshing sleep.

Biological, genetic, infectious and psychological mechanisms have been proposed for the development and persistence of symptoms but the etiology of CFS is not understood and may have multiple causes. There is no diagnostic laboratory test or biomarker for CFS. Symptoms of CFS include post-exertional malaise; unrefreshing sleep; widespread muscle and joint pain; sore throat; headaches of a type not previously experienced; cognitive difficulties; chronic, often severe, mental and physical exhaustion; and other characteristic symptoms in a previously healthy and active person. Persons with CFS may report additional symptoms such as muscle weakness, increased sensitivity to light, sounds and smells, orthostatic intolerance, digestive disturbances, depression, and cardiac and respiratory problems. It is unclear if these symptoms represent co-morbid conditions or are produced by an underlying etiology of CFS. CFS symptoms vary from person to person in number, type, and severity.

The majority of CFS cases start suddenly, usually accompanied by a “flu-like illness” while a significant proportion of cases begin within several months of severe adverse stress. An Australian prospective study found that after infection by viral and non-viral pathogens, a sub-set of individuals met the criteria for CFS, with the researchers concluding that “post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to CFS”. However, accurate prevalence and exact roles of infection and stress in the development of CFS are currently unknown.

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SECTION OVERVIEW

15.7: Microbial Diseases of the Cardiovascular and Lymphatic Systems

15.7A: Functions of the Lymphatic System

15.7B: The Cardiovascular System

15.7C: Structure of the Lymphatic System

15.7D: Cardiovascular and Lymphatic System Defenses

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15.7A: Functions of the Lymphatic System

The lymphatic system plays a prominent role in immune function, fatty acid absorption, and removal of interstitial fluid from tissues.

Learning Objectives

- Describe the roles of the lymphatic system

Key Points

- The lymphatic system is a linear network of lymphatic vessels and secondary lymphoid organs. It is the site of many immune system functions as well as its own functions.
- It is responsible for the removal of interstitial fluid from tissues into lymph fluid, which is filtered and brought back into the bloodstream through the subclavian veins near the heart.
- Edema accumulates in tissues during inflammation or when lymph drainage is impaired.
- It absorbs and transports fatty acids and fats as chylomicrons from the digestive system.
- It transports white blood cells and dendritic cells to lymph nodes where adaptive immune responses are often triggered.
- Tumors can spread through lymphatic transport.

Key Terms

- **lacteal**: A lymphatic capillary that absorbs dietary fats in the villi of the small intestine.
- **interstitial fluid**: Also called tissue fluid, a solution that bathes and surrounds the cells of multicellular animals.
- **white blood cell**: A type of blood cell involved with an immune response. Many white blood cells (primarily lymphocytes) are transported by the lymphatic system.

The lymphatic system is the site of many key immune system functions. It is important to distinguish that immune system functions can happen almost anywhere in the body, while the lymphatic system is its own system where many immune system functions take place. Besides immune system function, the lymphatic system has many functions of its own. It is responsible for the removal and filtration of interstitial fluid from tissues, absorbs and transports fatty acids and fats as chyle from the digestive system, and transports many of the cells involved in immune system function via lymph.

Removal of Fluid

Interstitial fluid accumulates in the tissues, generally as a result of the pressure exerted from capillaries (hydrostatic and osmotic pressure) or from protein leakage into the tissues (which occurs during inflammation). These conditions force fluid from the capillaries into the tissues. One of the main functions of the lymphatic system is to drain the excess interstitial fluid that accumulates.

The lymphatic system is a blunt-ended linear flow system, in which tissue fluids, cells, and large extracellular molecules, collectively called lymph, are drained into the initial lymphatic capillary vessels that begin at the interstitial spaces of tissues and organs. They are then transported to thicker collecting lymphatics, which are embedded with multiple lymph nodes, and are eventually returned to the blood circulation through the left and right subclavian veins and into the vena cava. They drain into venous circulation because there is lower blood pressure in veins, which minimizes the impact of lymph cycling on blood pressure. Lymph nodes located at junctions between the lymph vessels also filter the lymph fluid to remove pathogens and other abnormalities.

Fluid removal from tissues prevents the development of edema. Edema is any type of tissue swelling from increased flow of interstitial fluid into tissues relative to fluid drainage. While edema is a normal component of the inflammation process, in some cases it can be very harmful. Cerebral and pulmonary edema are especially problematic, which is why lymph drainage is so important. Abnormal edema can still occur if the drainage components of the lymph vessels are obstructed.

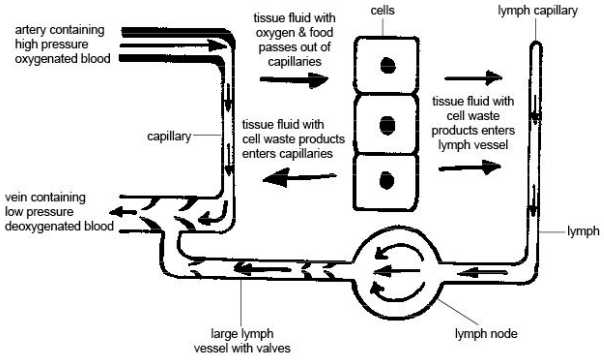

Figure: **The lymphatic system**: A diagram of fluid movement in the lymphatic system.

Fatty Acid Transport

The lymphatic system also facilitates fatty acid absorption from the digestive system. During fat digestion, fatty acids are digested, emulsified, and converted within intestinal cells into a lipoprotein called chylomicrons. Lymph drainage vessels that line the intestine, called lacteals, absorb the chylomicrons into lymph fluid. The lymph vessels then take the chylomicrons into blood circulation, where they react with HDL cholesterols and are then broken down in the liver.

Immune Cell Transport

In addition to tissue fluid homeostasis, the lymphatic system serves as a conduit for transport of cells involved in immune system function. Most notably, highly-specialized white blood cells called lymphocytes and antigen -presenting cells are transported to regional lymph nodes, where the immune system encounters pathogens, microbes, and other immune elicitors that are filtered from the lymph fluid. Much of the adaptive immune system response, which is mediated by dendritic cells, takes place in the lymph nodes. Lymphatic vessels, which uptake various antigens from peripheral tissues, are positively regulated by chemokines/cytokines secreted by various immune cells during inflammation. This allows antigens to enter lymph nodes, where dendritic cells can present them to lymphocytes to trigger an adaptive immune response.

While the lymphatic system is important for transporting immune cells, its transport capabilities can also provide a pathway for the spread of cancer. Lymph circulation is one of the main ways that tumors can spread to distant parts of the body, which is difficult to prevent.

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15.7B: The Cardiovascular System

Both the cardiovascular system and the lymphatic system are susceptible to diseases caused by microorganisms.

Learning Objectives

- Compare and contrast the causes associated with: endocarditis, myocarditis, bacteremia, vasculitis and lymphatic disease

Key Points

- Two common cardiovascular diseases caused by infection with microorganisms are endocarditis and myocarditis.
- Endocarditis is inflammation of the inner tissue of the heart such as its valves caused by infectious agents.
- Myocarditis is inflammation of heart muscle and it is most often due to infection by common viruses.
- Bacteremia is the presence of bacteria in the blood.
- Vasculitis is inflammation of the vessel wall due to an infection or autoimmune disease.
- Lymphadenopathy is a disease of the lymph nodes due to infection, auto- immune disease, or malignancy.

Key Terms

- **Endocarditis**: An inflammation of the endocardium and possibly the heart valves.
- **myocarditis**: Inflammation of the myocardium.
- **lymphadenopathy**: An abnormal enlargement of the lymph nodes
- **Vasculitis**: Inflammation of the vessel wall due to an infection or autoimmune disease.
- **bacteremia**: The presence of bacteria in the blood.

Both the cardiovascular system and the lymphatic system are susceptible to diseases caused by microorganisms.

In the cardiovascular system, the heart, the blood vessels (arteries, capillaries, and veins), and the blood are targets of pathogens. Two common cardiovascular diseases caused by infection with microorganisms are endocarditis and myocarditis.

1. Endocarditis is inflammation of the inner tissue of the heart such as its valves caused by infectious agents. The agents are usually bacterial, but other organisms can also be responsible. Since, the valves of the heart do not receive any dedicated blood supply, the defensive immune mechanisms (such as white blood cells) cannot directly reach the valves via the bloodstream. The lack of blood supply to the valves also has implications for treatment, since drugs also have difficulty reaching the infected valve.
2. Myocarditis or inflammatory cardiomyopathy is inflammation of heart muscle (myocardium) and it is most often due to infection by common viruses, such as parvovirus B19. It is often caused by an autoimmune reaction. Streptococcal M protein and coxsackievirus B have regions (epitopes) that are immunologically similar to cardiac myosin. During and after the viral infection, the immune system may attack cardiac myosin. Because a definitive diagnosis requires a heart biopsy, which doctors are reluctant to do because they are invasive, statistics on the incidence of myocarditis vary widely. The consequences of myocarditis thus also vary widely. It can cause a mild disease without any symptoms that resolves itself, or it may cause chest pain, heart failure, or sudden death. As most viral infections cannot be treated with directed therapy, symptomatic treatment is the only form of therapy for those forms of myocarditis. In the acute phase, supportive therapy, including bed rest, is indicated. For symptomatic patients, digoxin and diuretics provide clinical improvement.

Bacteremia is the presence of bacteria in the blood. Bacteria can enter the bloodstream as a severe complication of infections (like pneumonia or meningitis), during surgery (especially when involving mucous membranes such as the gastrointestinal tract), or due to catheters and other foreign bodies entering the arteries or veins (including intravenous drug abuse). Bacteremia can have several consequences. The immune response to the bacteria can cause sepsis and septic shock, which has a relatively high mortality rate. Bacteria can also use the blood to spread to other parts of the body (which is called hematogenous spread), causing infections away from the original site of infection. Examples include endocarditis or osteomyelitis. Treatment is with antibiotics, and prevention with antibiotic prophylaxis can be given in situations where problems are to be expected.

Vasculitis is inflammation of the vessel wall due to an infection (or autoimmune disease). Blood vessel permeability is increased in inflammation. Damage, due to trauma or spontaneously, may lead to hemorrhage due to mechanical damage to the vessel endothelium.

Lymphatic disease is a class of disorders that directly affect the components of the lymphatic system. Lymphadenopathy is a term meaning disease of the lymph nodes due to infection, auto-immune disease, or malignancy. Enlarged lymph nodes are a common symptom in a number of infectious diseases, of which some are as follows:

1. Acute infection (e.g., bacterial, or viral), or chronic infections (tuberculous lymphadenitis, cat-scratch disease).
2. The most distinctive symptom of bubonic plague is extreme swelling of one or more lymph nodes that bulge out of the skin as “buboes. ” The buboes often become necrotic and may even rupture.
3. Infectious mononucleosis is an acute viral infection, the hallmark of which is marked enlargement of the cervical lymph nodes.
4. It is also a symptom of cutaneous anthrax, measles and Human African trypanosomiasis, the latter two giving lymphadenopathy in lymph nodes in the neck.
5. Toxoplasmosis, a parasitic disease, gives a generalized lymphadenopathy.

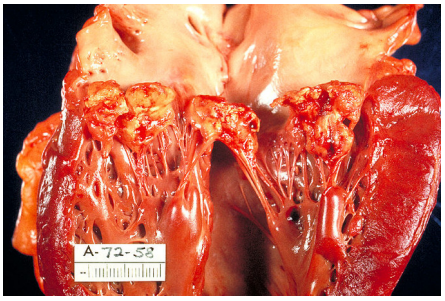

Figure: **Endocarditis**: A mitral valve vegetation caused by bacterial endocarditis.

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15.7C: Structure of the Lymphatic System

The lymphatic system consists of lymphatic vessels and associated lymphoid organs.

Learning Objectives

- Describe the structure and function of the lymphatic system

Key Points

- The lymphatic system is a circulatory system that drains fluid from the blood vessels.
- Lymph vessels are the site of fluid drainage and pump lymph fluid using smooth muscle and skeletal muscle action. The larger vessels contain valves to prevent backflow and pump towards the heart to return lymph fluid to the bloodstream by the subclavian veins.
- A lymph node is an organized collection of lymphoid tissue through which the lymph passes on its way to returning to the blood. Lymph nodes are located at intervals along the lymphatic system.
- Lymphoid tissue contains lymphocytes and other specialized cells and tissues that have immune system functions.

Key Terms

- **lymph node**: Small oval bodies of the lymphatic system, distributed along the lymphatic vessels clustered in the armpits, groin, neck, chest, and abdomen. They filter through lymph fluid.
- **lymph**: A colorless, watery, bodily fluid carried by the lymphatic system, consisting mainly of white blood cells.

The lymphatic system is a collection of structures and vessels that drains lymph from blood and has several other functions. It is a circulatory system for lymph fluid and the site of many key immune system functions.

Lymphatic Vessels

The lymphatic vessels are the lymphatic system equivalent of the blood vessels of the circulatory system and drain fluid from the circulatory system. The network of lymph vessels consists of the initial collectors of lymph fluid, which are small, valveless vessels, and goes on to form the precollector vessels, which have rudimentary valves that are not fully functional. These structures then form increasingly larger lymphatic vessels which form colaterals and have lymph-angions (lymph hearts). The larger lymph vessels contain valves that prevent the backflow of lymph.

The lymphatic system is an active pumping system driven by segments that have a function similar to peristalsis. They lack a central pump (like the heart in the cardio vascular system), so smooth muscle tissue contracts to move lymph along through the vessels. Skeletal muscle contractions also move lymph through the vessels. The lymphatic vessels make their way to the lymph nodes, and from there the vessels form into trunks. In general, the lymph vessels bring lymph fluid toward the heart and above it to the subclavian veins, which enable lymph fluid to re-enter the circulatory system through the vena cava.

Lymphatic Tissues and Organs

Lymphoid tissue is found in many organs including the lymph nodes, as well as in the lymphoid follicles in the pharynx such as the tonsils. Lymph nodes are found primarily in the armpits, groin, chest, neck, and abdomen. Lymphoid tissues contain lymphocytes (a type of highly differentiated white blood cell), but they also contain other types of cells for structural and functional support, such as the dendritic cells, which play a key role in the immune system. The system also includes all the structures dedicated to the circulation and production of lymphocytes, including the spleen, thymus, and bone marrow.

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15.7D: Cardiovascular and Lymphatic System Defenses

The circulatory system has a defence against microbial invaders in the form of the lymphatic system.

Learning Objectives

- Summarize the role of the lymphatic system during an infection

Key Points

- The lymphatic system works in close cooperation with other body systems to destroy pathogens and filter waste.
- The lymphatic system contains immune cells called lymphocytes, which protect the body against antigens (viruses, bacteria, etc.) that invade the body. Lymph nodes are sites of both microbial destruction and the production of antibodies against other foreign invaders.
- While the lymph system acts as a defence against microbial invaders it can also cause problems. Notably over-swelling, and acting as a home for bacterial invaders, even spreading bacteria or cancerous cells.
- Lymph is the fluid that is formed when interstitial fluid enters the initial lymphatic vessels of the lymphatic system and transports antigen-presenting cells (APCs), such as dendritic cells, to the lymph nodes where an immune response is stimulated.

Key Terms

- **lymphatic system**: In mammals, including humans, a network of lymph vessels and lymph nodes that transport fluid, fats, proteins, and lymphocytes to the bloodstream as lymph, and remove microorganisms and other debris from tissues.
- **lymphocytes**: type of white blood cells in the vertebrate immune system

The cardiovascular and lymphatic are both integral parts of the circulatory system. The cardiovascular system basically moves blood throughout the body. While the lymphatic system is part of the circulatory system, comprising a network of conduits called lymphatic vessels. Rather than blood the lymph systems carries a clear fluid called lymph (from Latin *lympha*, meaning “water goddess”) unidirectionally towards the heart. The lymph system is not a closed system. The circulatory system processes an average of 20 liters of blood per day through capillary filtration which removes plasma while leaving the blood cells. While the circulatory system is essential for survival, it also is the source of a major problem when dealing with microbial infections. Many microbes take advantage of the circulatory system to spread throughout the body. Not surprising then the lymphatic system is critical for the bodies immune response to microbial infections. Lymphatic organs play an important part in the immune system, having a considerable overlap with the lymphoid system. Lymphoid tissue is found in many organs, particularly the lymph nodes, and in the lymphoid follicles associated with the digestive system such as the tonsils. Lymphoid tissues contain lymphocytes, but they also contain other types of cells for support. The system also includes all the structures dedicated to the circulation and production of lymphocytes (the primary cellular component of lymph), which includes the spleen, thymus, bone marrow, and the lymphoid tissue associated with the digestive system.

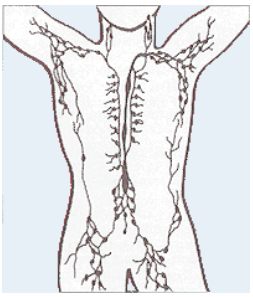

Figure: **The lymphatic system**: This diagram shows the network of lymph nodes and connecting lymphatic vessels in the human body.

As well as filtering the lymph, lymph nodes produce the white cells known as lymphocytes. Lymphocytes are also produced by the thymus, spleen and bone marrow. There are two kinds of lymphocyte. The first attach invading micro organisms directly while others produce antibodies that circulate in the blood and attack them. When micro-organisms invade the body, or the body encounters antigens (such as pollen), antigens are transported to the lymph. Lymph is carried through the lymph vessels to regional lymph nodes. In the lymph nodes, the macrophages and dendritic cells phagocytose the antigens, process them, and present the antigens to lymphocytes, which can then start producing antibodies or serve as memory cells. The function of memory cells is to

recognize specific antigens in the future. The function of the lymphatic system can therefore be summarized as transport and defense. It is important for returning the fluid and proteins that have escaped from the blood capillaries to the blood system and is also responsible for picking up the products of fat digestion in the small intestine. Its other essential function is as part of the immune system, defending the body against infection.

While the lymph nodes do battle infections, there are problems with lymph nodes and the lymphatic system. During infection of the body the lymph nodes often become swollen and tender because of their increased activity. This is what causes the swollen 'glands' in your neck during throat infections, mumps and tonsillitis. Sometimes the bacteria multiply in the lymph node and cause inflammation. Cancer cells may also be carried to the lymph nodes and then transported to other parts of the body where they may multiply to form a secondary growth or metastasis. The lymphatic system may therefore contribute to the spread of cancer. Inactivity of the muscles surrounding the lymphatic vessels or blockage of these vessels causes tissue fluid to 'back up' in the tissues resulting in swelling or edema.

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SECTION OVERVIEW

15.8: Bacterial Diseases of the Cardiovascular and Lymphatic Systems

Topic hierarchy

15.8A: Sepsis and Septic Shock

15.8B: Bacterial Infections of the Heart

15.8C: Rheumatic Fever

15.8D: Tularemia

15.8E: Brucellosis (Undulant Fever)

15.8F: Anthrax

15.8G: Gangrene

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15.8A: Sepsis and Septic Shock

Septic shock occurs when a body's response to an infection (sepsis) leads to life-threatening low blood pressure.

Learning Objectives

- Compare and contrast the symptoms of: sepsis, severe sepsis, septic shock

Key Points

- Sepsis results from certain bacterial infections, often acquired in a hospital. Having certain conditions, such as a weakened immune system, certain chronic disorders, an artificial joint, or heart valve increases the risk.
- Symptoms of sepsis include either fever or low body temperature, rapid breathing, chills and shaking, rapid heartbeat, decreased urine output, and confusion or delirium.
- Severe sepsis often causes extremely low blood pressure, which limits blood flow to the body and can result in organ failure and death. This is known as septic shock.
- Sepsis is treated with antibiotics, fluids, and medicines to support blood pressure and prevent organ damage.

Key Terms

- **septic shock**: A life-threatening condition caused by infection and sepsis, often after surgery or trauma.
- **sepsis**: A life-threatening medical condition caused by a severe inflammatory response of the human body triggered by the presence of an infectious agent.
- **mortality rate**: the number of deaths per given unit of population over a given period of time

Sepsis is a potentially deadly medical condition characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) that is triggered by an infection. Septic shock is a medical condition as a result of severe infection and sepsis, though the microbe may be systemic or localized to a particular site. Its most common victims are children, immuno-compromised individuals, and the elderly, as their immune systems cannot deal with the infection as effectively as those of healthy adults. Frequently, patients suffering from septic shock are cared for in intensive care units. The mortality rate from septic shock is approximately 25–50%.

Sepsis

Sepsis is an illness in which the body has a severe response to bacteria or other germs. The body may develop this inflammatory response by the immune system to microbes in the blood, urine, lungs, skin, or other tissues. A popular term for sepsis is blood poisoning. Severe sepsis is the systemic inflammatory response, infection, and the presence of organ dysfunction.

A bacterial infection anywhere in the body may set off the response that leads to sepsis. Common places where an infection might start include:

- the bloodstream
- bones (common in children)
- the bowel (usually seen with peritonitis)
- the kidneys (upper urinary tract infection or pyelonephritis)
- the lining of the brain (meningitis)
- the liver or gallbladder
- the lungs (bacterial pneumonia)
- the skin (cellulitis)

For patients in the hospital, common sites of infection include intravenous lines, surgical wounds, surgical drains, and sites of skin breakdown known as bedsores (decubitus ulcers).

The therapy of sepsis rests on intravenous fluids, antibiotics, surgical drainage of infected fluid collections, and appropriate support for organ dysfunction. This may include hemodialysis in kidney failure, mechanical ventilation in pulmonary dysfunction, transfusion of blood products, and drug and fluid therapy for circulatory failure. Ensuring adequate nutrition—preferably by enteral feeding, but if necessary by parenteral nutrition—is important during prolonged illness.

Septic Shock

In sepsis, blood pressure drops, resulting in septic shock. Major organs and body systems, including the kidneys, liver, lungs, and central nervous system, stop working properly because of poor blood flow.

Most cases of septic shock are caused by Gram-positive bacteria, followed by endotoxin-producing Gram-negative bacteria. Endotoxins are bacterial membrane lipopolysaccharides (LPS) consisting of a toxic fatty acid (lipid A) core common to all Gram-negative bacteria, and a complex polysaccharide coat (including O antigen) unique for each species. Analogous molecules in the walls of Gram-positive bacteria and fungi can also elicit septic shock. In Gram-negative sepsis, free LPS attaches to a circulating LPS-binding protein, and the complex then binds to a specific receptor (CD14) on monocytes, macrophages, and neutrophils.

If sepsis worsens to the point of end-organ dysfunction (renal failure, liver dysfunction, altered mental status, or heart damage) then the condition is called severe sepsis. Once severe sepsis worsens to the point where blood pressure can no longer be maintained with intravenous fluids alone, then the criteria have been met for septic shock. The precipitating infections which may lead to septic shock if severe enough include appendicitis, pneumonia, bacteremia, diverticulitis, pyelonephritis, meningitis, pancreatitis, and necrotizing fasciitis.



Figure: **Sepsis**: Sepsis due to meningococcal disease.

Treatment primarily consists of the following:

1. Volume resuscitation
2. Early antibiotic administration
3. Early goal directed thearpy
4. Rapid source identification and control.
5. Support of major organ dysfunction.

There are new drugs that act against the extreme inflammatory response seen in septic shock. These may help limit organ damage.

The mortality rate from sepsis is approximately 40% in adults, and 25% in children, and is significantly greater when left untreated for more than seven days.

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15.8B: Bacterial Infections of the Heart

Bacterial endocarditis is an infection of the inner surface of the heart or heart valves caused by the presence of bacteria in the blood.

Learning Objectives

- Recognize the causes and treatments for endocarditis

Key Points

- Endocarditis occurs when bacteria grow on the edges of a heart defect or on the surface of an abnormal valve after the bacteria enter the blood stream, most commonly from dental procedures but also from procedures involving the gastrointestinal or urinary tract.
- The most important diagnostic test for endocarditis involves a positive blood culture. A blood culture is a small sample of blood drawn from the vein which is grown in a special solution so that bacteria can be detected.
- Symptoms and signs of endocarditis vary but include prolonged fever poor appetite, feeling weak or tired, joint pains, skin rashes, and changes in the nature of a previously present heart murmur.
- Treatment of bacterial endocarditis consists of a period of intravenous doses of appropriate antibiotics determined from blood tests under the supervision of an infectious disease specialist and cardiologist.

Key Terms

- **Endocarditis**: An inflammation of the interior lining of the heart or the endocardium and possibly the heart valves (pathology, cardiology).
- **bacteremia**: The medical condition of having bacteria in the bloodstream.

In a healthy individual, a bacteremia (where bacteria get into the blood stream through a minor cut or wound) would normally be cleared quickly with no adverse consequences. If a heart valve is damaged and covered with a piece of blood clot, the valve provides a place for the bacteria to attach themselves and an infection can be established. Endocarditis, or inflammation of the inner tissue of the heart, occurs as a result. The valves of the heart do not receive any dedicated blood supply. As a result, defensive immune mechanisms (such as white blood cells) cannot directly reach the valves via the bloodstream. When bacteria attaches to a valve surface and forms a vegetation, the host immune response is blunted. The lack of blood supply to the valves also has implications for treatment, since drugs also have difficulty reaching the infected valve. Normally, blood flows smoothly through these valves. If they have been damaged – from rheumatic fever, for example – the risk of bacterial attachment is increased.

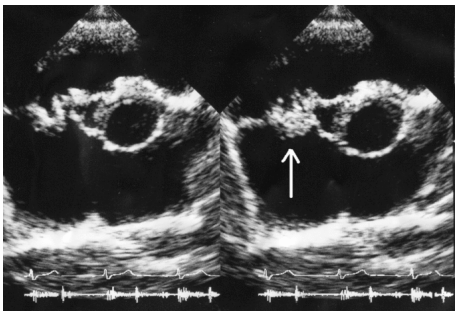

Figure: **Endocarditis ultrasound**: Vegetation on tricuspid valve by echocardiography. Arrow denotes the vegetation.

Bacteremia caused by dental procedures (in most cases due to streptococci viridans, which reside in oral cavity), such as a cleaning or extraction of a tooth and from procedures involving the gastrointestinal or urinary tract can cause bacterial endocarditis. Intravenous drug abuse may also cause bacterial endocarditis from the aseptic introduction of skin bacteria.

Symptoms and signs of endocarditis vary, but prolonged fever (more then 2-3 days) without an obvious cause is a most important sign and should always be investigated in a child with congenital heart disease. Other signs and symptoms include poor appetite, feeling weak or tired, joint pains, skin rashes, and changes in the nature of a previously present heart murmur. The chance that these signs and symptoms are caused by endocarditis is more likely if they occur soon after a dental cleaning or procedure involving the gastrointestinal or urinary tract.

High dose antibiotics are administered by the intravenous route to maximize diffusion of antibiotic molecules into vegetation(s) from the blood filling the chambers of the heart. This is necessary because neither the heart valves nor the vegetations adherent to them are supplied by blood vessels. Antibiotics are continued for a long time, typically two to six weeks depending on the characteristics of the infection and the causative microorganisms.

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15.8C: Rheumatic Fever

Rheumatic fever is an inflammatory disease that can develop as a complication of inadequately treated strep throat.

Learning Objectives

- Outline the effect of infection by Steptococcus pyogenes on the immune system

Key Points

- Rheumatic fever is a condition that is a complication of untreated strep throat. Strep throat is caused by a group A streptococcal infection found in the throat.
- When the body senses the strep infection, it sends antibodies to fight it and sometimes these antibodies attack the tissues of your joints or heart instead. This is known as anitbody cross-reactivity which leads to rheumatic fever.
- Symptoms of rheumatic fever occur several weeks after initial throat problems have disappeared; and include chest pain, fever, heart problems, joint pain, nosebleeds, and skin rash.
- Rheumatic fever is treated using a combination of antibiotics and anti-inflammatory medications.

Key Terms

- **rheumatism**: Any disorder of the muscles, tendons, joints, bones, nerves, characterized by pain, discomfort and disability.
- **Streptococcus**: A spherical, gram-positive bacterium of the genus Streptococcus. Although commonly found benignly in the human mouth and gut, and though many species are non-pathogenic, other species can cause diseases including strep throat and more serious conditions.

Rheumatic fever is an inflammatory disease that occurs following a *Streptococcus pyogenes* infection, such as streptococcal pharyngitis (strep throat) or scarlet fever, that affects the peri-arteriolar connective tissue. Believed to be caused by antibody cross-reactivity that can involve the heart, joints, skin, and brain; the illness typically develops two to three weeks after a streptococcal infection.

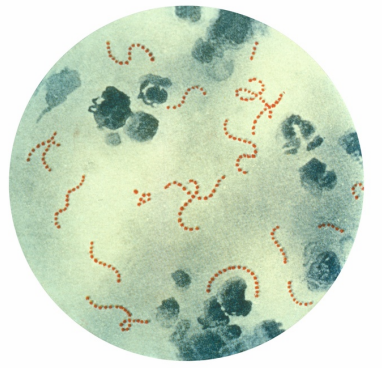

Figure: **Streptococcus pyogenes bacteria**: Photomicrograph of Streptococcus pyogenes bacteria, 900x Mag. A pus specimen, viewed using Pappenheim's stain. Last century, infections by S. pyogenes claimed many lives especially since the organism was the most important cause of puerperal fever and scarlet fever.

Acute rheumatic fever commonly appears in children between the ages of six and 15, with only 20% of first-time attacks occurring in adults. The illness is so named because of its similarity in presentation to rheumatism.

This cross-reactivity is a Type II hypersensitivity reaction and is termed *molecular mimicry.* During a Streptococcus infection, mature antigen -presenting cells, such as B cells, present the bacterial antigen to CD4-T cells which differentiate into helper T_2cells. In turn, Helper T_2 cells activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus. However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever.

Diagnosis of rheumatic fever can be made when two of the major criteria, or one major plus two minor criteria, are present along with evidence of streptococcal infection.

The major criteria for diagnosis include:

- Arthritis in several large joints (polyarthritis)
- Heart inflammation (carditis)
- Nodules under the skin (subcutaneous skin nodules)
- Rapid, jerky movements (chorea, Sydenham chorea)
- Skin rash (erythema marginatum)

Minor Criteria:

- Fever of 38.2–38.9 °C (101–102 F)
- Arthralgia: Joint pain without swelling (Cannot be included if polyarthritis is present as a major symptom)
- Raised erythrocyte sedimentation rate or C reactive protein
- Leukocytosis
- ECG showing features of heart block, such as a prolonged PR interval (Cannot be included if carditis is present as a major symptom)
- Previous episode of rheumatic fever or inactive heart disease.

Acute rheumatic fever is treated with antibiotics and anti-inflammatory medications such as aspirin and corticosteroids.

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15.8D: Tularemia

Tularemia is an infection caused by the Gram-negative bacteria *Francisella tularensis*.

Learning Objectives

- Recall the mode of transmission and symptoms associated with tularemia

Key Points

- Tularemia is an infection common in wild rodents that is passed to humans through contact with infected animal tissues or by ticks, biting flies, and mosquitoes.
- Symptoms vary depending upon the site of infection. The main clinical signs include fever, lethargy, anorexia, muscle pains and signs of septicemia.
- Although tularemia can be life-threatening, most infections can be treated successfully with antibiotics.

Key Terms

- **Francisella tularensis**: Francisella tularensis is a pathogenic species of gram-negative bacteria and the causative agent of tularemia or rabbit fever.
- **macrophage**: A white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink. It presents foreign antigens on MHC II to lymphocytes. Part of the innate immune system.
- **tularemia**: An infectious disease caused by the bacterium Francisella tularensis.

Tularemia (also known as Pahvant Valley plague, rabbit fever, deer fly fever, and Ohara's fever) is a serious infectious disease caused by the bacterium *Francisella tularensis*. A Gram-negative, nonmotile coccobacillus, the bacterium has several subspecies with varying degrees of virulence.

The most important of these is *F. tularensis tularensis* (Type A), which is found in lagomorphs (rabbits and similar animals) in North America, and it is highly virulent in humans and domestic rabbits. *F. tularensis palaearctica* (Type B) occurs mainly in aquatic rodents (beavers, muskrats) in North America and in hares and small rodents in northern Eurasia. It is less virulent for humans and rabbits.

The primary vectors are ticks and deer flies, but the disease can also be spread through other arthropods. The disease is named after Tulare County, California and most commonly occurs in North America and parts of Europe and Asia. Although outbreaks can occur in the United States, they are rare.

Depending on the site of infection, tularemia has six characteristic clinical symptoms: ulceroglandular, glandular, oropharyngeal, pneumonic, oculoglandular, and typhoidal. The incubation period for tularemia is one to 14 days; most human infections become apparent after three to five days.



Figure: **Tularemia Lesion**: A Tularemia lesion on the dorsal skin of right hand. Tularemia is caused by the bacterium, Francisella tularensis. Symptoms vary depending on how the person was exposed to the disease and, as is shown here, can include skin ulcers.

In most susceptible mammals, the clinical signs include fever, lethargy, anorexia, signs of septicemia, and possibly, death. Fever is moderate or very high. Tularemia bacilli can be isolated from blood cultures at this stage. The face and eyes redden and become inflamed. Inflammation spreads to the lymph nodes, which enlarge and may suppurate (mimicking bubonic plague), accompanied by a high fever. Death occurs in less than 1% if therapy is initiated promptly.

Francisella tularensis is an intracellular bacterium, meaning it is able to live as a parasite within host cells. It primarily infects macrophages and is able to evade the immune system. The course of disease involves the spread of the organism to multiple organ systems, including the lungs, liver, spleen, and lymphatic system; and differs according to the route of exposure.

Tularemia is primarily treated with streptomycin but can also be treated with gentamicin for ten days and tetracycline-class drugs such as doxycycline for two to three weeks, chloramphenicol, or fluoroquinolones. An attenuated, live vaccine is available, but its use is only for high-risk groups.

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15.8E: Brucellosis (Undulant Fever)

Brucellosis is an infectious disease that occurs from contact with animals carrying *Brucella* bacteria.

Learning Objectives

- Recognize the causes and symptoms of brucellosis

Key Points

- Brucella can infect cattle, goats, dogs, and pigs. The bacteria can spread to humans by ingesting unsterilized milk or meat from infected animals, or close contact with their secretions.
- Brucellosis symptoms include fever, joint pain and fatigue. The infection can usually be treated successfully with antibiotics.
- People working in jobs where they often come in contact with animals or meat such as slaughterhouse workers, farmers, and veterinarians are at higher risk for contracting Brucellosis.

Key Terms

- **brucellosis**: Disease caused by the bacterium, Brucella, which is carried by ruminants. Symptoms include recurring fevers, sweating, weakness, anorexia, headaches, depression and generalized aches and pains.
- **Brucella**: A genus of Gram-negative bacteria. They are small, non-motile, non-encapsulated coccobacilli, which function as facultative intracellular parasites.

Brucellosis, also called Bang's disease, Crimean fever, Gibraltar fever, Malta fever, Maltese fever, Mediterranean fever, rock fever, or undulant fever, is a highly-contagious zoonosis caused by ingestion of unsterilized milk or meat from infected animals or close contact with their secretions. Transmission from human to human, through sexual contact or from mother to child, is rare but possible.

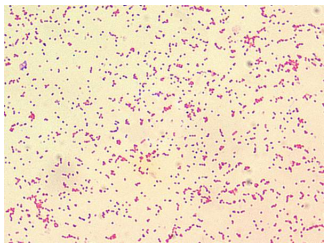

Figure: **Brucella bacteria**: Brucella spp. are poorly staining, small gram-negative coccobacilli.

Brucella spp. are small, gram-negative, non-motile, non-spore-forming, rod-shaped (coccobacilli) bacteria. They function as facultative intracellular parasites causing chronic disease, which usually persists for life. Symptoms include profuse sweating, and joint and muscle pain.

Species infecting domestic livestock are *B. melitensis* (goats and sheep), *B. suis* (pigs), *B. abortus* (cattle), *B. ovis* (sheep), and *B. canis* (dogs). *B. abortus* also infects bison and elk in North America and *B. suis* is endemic in caribou. *Brucella* species have also been isolated from several marine mammal species (pinnipeds and cetaceans).

Brucellosis in humans is usually associated with the consumption of unpasteurized milk and soft cheeses made from the milk of infected animals, primarily goats, infected with *Brucella melitensis*, as well as with occupational exposure of laboratory workers, veterinarians, and slaughterhouse workers. Some vaccines used in livestock, most notably *B. abortus strain 19*, also cause disease in humans if accidentally injected.

Brucellosis induces inconstant fevers, sweating, weakness, anaemia, headaches, depression, and muscular and bodily pain. The symptoms are like those associated with many other febrile diseases, but with emphasis on muscular pain and sweating.

The duration of the disease can vary from a few weeks to many months or even years. In the first stage of the disease, septicemia occurs and leads to the classic triad of undulant fevers, sweating (often with characteristic smell, likened to wet hay), and migratory arthralgia and myalgia.

Antibiotics like tetracyclines, rifampicin, and the aminoglycosides streptomycin and gentamicin are effective against Brucella bacteria. However, the use of more than one antibiotic is needed for several weeks, because the bacteria incubate within cells.

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15.8F: Anthrax

Anthrax is a rare, infectious disease caused by *Bacillus anthracis* that can spread from animals to humans.

Learning Objectives

- Discuss the causes and mode of transmission for anthrax including: inhalation, ingestion and direct entry through abrasions

Key Points

- Bacillus anthracis exists in the soil as spores. Spores are inactive forms of the bacteria and can survive for decades in this form.
- Humans can become infected through contact with the anthrax spores from infected animals. It is not conatgious and cannot be spread from one infected person to another person.
- There are three ways one can become infected with anthrax: by inhalation of anthrax spores, entrance of spores through cuts in the skin, and by eating undercooked meat containing anthrax spores.
- Anthrax can be successfully treated with early antibiotic treatment. An anthrax vaccine has been approved for use in humans and is effective in protecting against an anthrax infection.

Key Terms

- **Bacillus anthracis**: Bacillus anthracis is the etiologic agent of anthrax and the only obligate pathogen within the genus Bacillus. B. anthrais a Gram-positive, endospore-forming, rod-shaped bacterium, with a width of 1-1.2µm and a length of 3-5µm.It can be grown in an ordinary nutrient medium under aerobic or anaerobic conditions.
- **anthrax**: An infectious bacterial disease of herbivores than can also occur in humans through contact with infected animals, tissue from infected animals, or high concentrations of anthrax spores.

Anthrax is an acute disease caused by the bacterium *Bacillus anthracis*. Most forms of the disease are lethal, and it affects both humans and animals. Anthrax commonly infects wild and domesticated herbivorous mammals that ingest or inhale the spores while grazing. Carnivores living in the same environment may become infected by consuming infected animals. Humans become infected through contact with the anthrax spores from infected animals.

Bacillus anthracis is a rod-shaped, Gram-positive, aerobic bacterium about 1 by 9 micrometers in length. The bacterium normally rests in endospore form in the soil, and can survive for decades in this state. *B.anthracis* bacterial spores have been known to have reinfected animals over 70 years after burial sites of anthrax-infected animals were disturbed. Herbivores are often infected whilst grazing or browsing, especially when eating rough, irritant, or spiky vegetation. It has been hypothesized that the vegetation may cause wounds within the gastrointestinal tract, permitting entry of the bacterial endospores into the tissues. This has not been proven, however. Once ingested or placed in an open wound, the bacterium begins multiplying inside the animal or human and typically kills the host within a few days or weeks. The endospores germinate at the site of entry into the tissues and then spread via the circulation to the lymphatics, where the bacteria multiply.

There are three ways in which people can become infected by anthrax:

1. By inhaling contaminated air containing anthrax spores. This is known as inhalation anthrax or pulmonary anthrax and can cause serious, sometimes lethal respiratory disease. Symptoms are flu-like, but soon develop into nausea and severe breathing problems. Inhalation anthrax has a 97% mortality rate.
2. By handling infected animals and/or animal products, antrax spores can enter through cuts in the skin. This is known as cutaneous anthrax. It first appears as a boil-like lesion then eventually forms a painless ulcer with a black center. Death is rare when the appropriate antibiotics are used.
3. By eating undercooked meat containing anthrax spores. This is known as gastrointestinal antrax. This is rare, with only 2 cases reported in the United States. Symptoms include intestinal inflammation, nausea, loss of appetite, vomiting of blood, abdominal pain and severe diarrhea.

Anthrax can be treated with anitbiotics. The earlier the anthrax is treated, the higher the chance of survival. Treatment for anthrax infection and other bacterial infections includes large doses of intravenous and oral antibiotics, such as fluoroquinolones (like ciprofloxacin), doxycycline, erythromycin, vancomycin, or penicillin. FDA-approved agents include ciprofloxacin, doxycycline, and penicillin. In possible cases of inhalation anthrax, early antibiotic prophylaxis treatment is crucial to prevent possible death.

In the United States, the human anthrax vaccine is required for most US military units and civilian contractors assigned to homeland bioterrorism defense or deployed in Iraq, Afghanistan or South Korea.

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15.8G: Gangrene

Gangrene is a serious and potentially life-threatening condition that arises when a considerable mass of body tissue dies.

Learning Objectives

- Compare and contrast the different types of gangrene: dry, wet, gas, noma, fournier gangrene and necrotizing fasciitis

Key Points

- Gangrene may be caused by an infection, injury, or a complication of a long-term condition that restricts blood circulation.
- There are six main types of gangrene: dry gangrene, wet gangrene. gas gangrene, necrotizing fasciitis, Fournier's gangrene, and noma.
- Dead tissue cannot be saved, and amputation is necessary in most cases.

Key Terms

- **gangrene**: The death of tissue due to reduced blood supply as a result of infection or a blocked blood vessel.
- **necrosis**: The localized death of cells or tissues through injury, disease, or the interruption of blood supply.
- **debridement**: The removal of dead, damaged, or infected tissue to improve the healing potential of the remaining healthy tissue.

Gangrene is a serious and potentially life-threatening condition that arises when a considerable mass of body tissue dies. This may occur after an injury or infection, or in people suffering from chronic health problems affecting blood circulation. The primary cause of gangrene is reduced blood supply to the affected tissues, which results in necrosis, or cell death. Diabetes and long-term smoking increase the risk of suffering from gangrene.

There are different types of gangrene with different symptoms, including:

- Dry gangrene begins at the distal part of a limb due to ischemia (restriction of circulation), and often occurs in the toes and feet of elderly patients due to arteriosclerosis (hardening of the arteries). Dry gangrene spreads slowly until it reaches the point where the blood supply is adequate to keep tissue viable. The affected part is dry, shrunken, and dark reddish-black, resembling mummified flesh. The gangrenous tissue most often detaches spontaneously.
- Wet gangrene occurs in naturally moist tissue and organs such as the mouth, bowel, lungs, cervix, and vulva. Bedsores occurring on body parts such as the sacrum, buttocks, and heels are also categorized as wet gangrene infections. In wet gangrene, the tissue is infected by microorganisms that cause decay, in turn causing tissue to swell and emit a fetid smell. Wet gangrene usually develops rapidly due to blockage of blood flow, most commonly in veins. The affected part is saturated with stagnant blood, which promotes the rapid growth of bacteria. The toxic products formed by bacteria are absorbed, causing systemic manifestation of septicemia and finally death.
- Gas gangrene is a bacterial infection that produces gas within tissues. It is a deadly form of gangrene usually caused by *Clostridium perfringens* bacteria. Infection spreads rapidly as the gases produced by bacteria expand and infiltrate nearby healthy tissue. Because of its ability to quickly spread to surrounding tissues, gas gangrene should be treated as a medical emergency.
- Necrotizing fasciitis affects the deeper layers of the skin.
- Noma is a gangrene of the face.
- Fournier gangrene usually affects the male genitals and groin.

Treatment of gangrene is usually surgical debridement, wound care, and antibiotic therapy, though amputation is necessary in many cases.



Figure: **Dry Gangrene**: Gangrene of the 1st to 4th toes of the right foot of a person with diabetes.

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SECTION OVERVIEW

15.9: Viral Diseases of the Cardiovascular and Lymphatic Systems

Topic hierarchy

15.9A: Burkitt's Lymphoma

15.9B: Infectious Mononucleosis

15.9C: Other Diseases and Epstein-Barr Virus

15.9D: Cytomegalovirus Infections

15.9E: Chikungunya Fever

15.9F: Classic Viral Hemorrhagic Fevers

15.9G: Emerging Viral Hemorrhagic Fevers

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15.9A: Burkitt's Lymphoma

Burkitt's lymphoma is a very fast growing form of non-Hodgkin's lymphoma, a cancer in the lymphatic system.

Learning Objectives

- Distinguish between the three variants of Burkitt's lymphoma: endemic, sporadic and immunodeficiency-associated

Key Points

- Burkitt's lymphoma was first discovered in children in certain parts of Africa by surgeon Denis Parsons Burkitt, but also occurs in the United States.
- There are three types of Burkitt's lymphoma: endemic, the sporadic and the immunodeficiency-associated. The endemic type is closely associated with the Epstein-Barr virus (EBV), the main cause of infectious mononucleosis.
- Burkitt's lymphoma usually develops in the abdomen and spreads to other organs, including the brain. It may first be noticed as a swelling of the lymph nodes (glands) in the neck, groin, or under the arm.
- Chemotherapy and various drugs are used to treat this type of cancer.

Key Terms

- **lymph**: A colourless, watery, bodily fluid carried by the lymphatic system, that consists mainly of white blood cells.
- **lymphoma**: A malignant tumor that arises in the lymph nodes or in other lymphoid tissue.
- **Non-Hodgkin's lymphoma**: The non-Hodgkin lymphomas are a diverse group of blood cancers that include any kind of lymphoma, except cancers originating from white blood cells called lymphocytes.

Burkitt's lymphoma is a form of non-Hodgkin's lymphoma, a cancer of the lymphatic system (in particular, B lymphocytes). It is named after Denis Parsons Burkitt, a surgeon who first described the disease in 1956 while working in equatorial Africa. Burkitt's lymphoma usually develops in the abdomen and spreads to other organs, including the brain. Burkitt's lymphoma involves B-cells and is a rapidly growing cancer. Of all cancers involving the same class of blood cell, 2% of cases are Burkitt's lymphoma.

Classification

Currently Burkitt's lymphoma can be divided into three main clinical variants:

1. Endemic: This variant occurs in equatorial Africa. It is the most common malignancy affecting children in this area. Children affected with the disease often also have chronic malaria, which is believed to have reduced resistance to Epstein-Barr virus (EBV), allowing it to take hold. The disease characteristically involves the jaw or other facial bone, distal ileum, cecum, ovaries, kidney or the breast.
2. Sporadic: This variant type, also known as "non-African" is found outside of Africa. The tumor cells have a similar appearance to that of endemic Burkitt lymphoma. Again it is believed that impaired immunity provides an opening for development of the Epstein-Barr virus. The jaw is less commonly involved, compared to the endemic variant. The ileo-cecal region is the common site of involvement.
3. Immunodeficiency-associated: Immunodeficiency-associated Burkitt lymphoma is usually associated with HIV infection or occurs in the setting of post-transplant patients who are taking immunosuppressive drugs. Burkitt lymphoma can be one of the diseases associated with the initial manifestation of AIDS.

By morphology (i.e. microscopic appearance) or immunophenotype, it is almost impossible to differentiate these three clinical variants. Immunodeficiency-associated Burkitt lymphoma may demonstrate more plasmacytic appearance or more pleomorphism, but these features are not specific.



Figure: **Burkitt's Lymphoma**: Swelling of the jaw associated with Burkitt's Lymphoma

Symptoms and Treatment

Burkitt lymphoma may first be noticed as a swelling of the lymph nodes (glands) in the neck, groin, or under the arm. These swollen lymph nodes are often painless, but can grow very rapidly. In the types commonly seen in the United States, the cancer usually starts in the belly area (abdomen). The disease can also start in the ovaries, testes, brain, and spinal fluid. Symptoms include fever, night sweats, unexplained swollen lymph nodes, and unexplained weight loss.

Chemotherapy is used to treat this type of cancer. Commonly used medicines include prednisone, cyclophosphamide, doxorubicin, ifosfamide, vincristine, cytarabine, methotrexate, rituximab, and etoposide. Other treatments are immunotherapy, bone marrow transplants, stem cell transplant, surgery to remove the tumor, and radiotherapy.

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15.9B: Infectious Mononucleosis

Learning Objectives

- Describe infectious mononucleosis

Infectious mononucleosis is an infectious, widespread viral disease caused by the Epstein–Barr virus (EBV), one type of herpes virus, to which more than 90% of adults have been exposed. Occasionally, the symptoms can recur at a later period. It is sometimes colloquially known as the "kissing disease" from its oral transmission. Most people are exposed to the virus as children, when the disease produces no noticeable or only flu-like symptoms. In developing countries, people are exposed to the virus in early childhood more often than in developed countries. As a result, the disease in its observable form is more common in developed countries. It is most common among adolescents and young adults.

Symptoms

The disease is characterized by fever, sore throat, and fatigue, along with several other possible signs and symptoms, especially in adolescents and young adults. The infection is spread via saliva and has an incubation period of four to seven weeks. Symptoms usually persist for two to three weeks, but fatigue is often more prolonged. Infectious mononucleosis is primarily diagnosed by observation of symptoms, but suspicion can be confirmed by several diagnostic tests. The most commonly used diagnostic criterion is the presence of 50% lymphocytes with at least 10% atypical lymphocytes (large, irregular nuclei), while the person also has fever, pharyngitis, and adenopathy. Infectious mononucleosis is generally self-limiting, so only symptomatic and/or supportive treatments are used. Rest is recommended during the acute phase of the infection.

Once the acute symptoms of an initial infection disappear, they often do not return. But once infected, the patient carries the virus for the rest of his or her life. The virus typically lives dormantly in B lymphocytes. Independent infections of mononucleosis may be contracted multiple times, regardless of whether the patient is already carrying the virus dormantly.

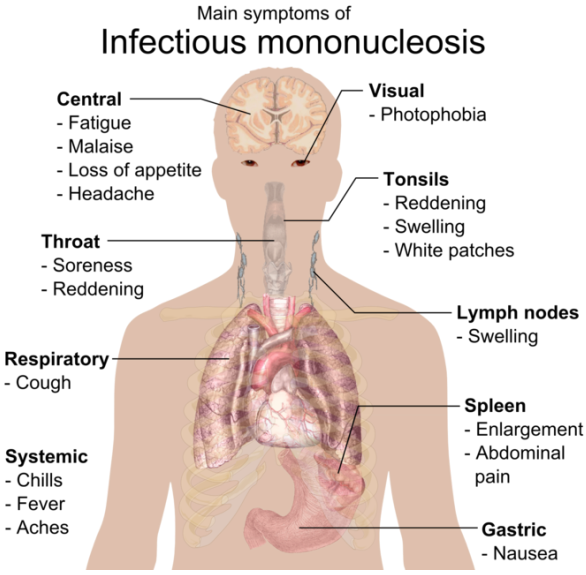

Figure: **Main Symptoms of Infectious Mononucleosis**: This graph illustrates the location of the symptoms.

Key Points

- Infectious mononucleosis is an infectious disease caused by the Epstein-Barr virus (EBV).
- Infectious mononucleosis (also called mono or kissing disease) is spread orally and is characterized by symptoms such as fever, sore throat, and fatigue.
- Once infected, the virus lives dormantly in B lymphocytes in a person.

Key Terms

- **Epstein-Barr virus (EBV)**: Virus responsible for causing infectious mononucelosis.

- **infectious mononucleosis**: An infectious, widespread viral disease caused by the Epstein–Barr virus (EBV), one type of herpes virus. Most people are exposed to the virus as children, when the disease produces no noticeable or only flu-like symptoms.

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15.9C: Other Diseases and Epstein-Barr Virus

Learning Objectives

- Distinguish between the lytic replicative and latency cycle of the Epstein-Barr virus infection cycle and discuss the prevalence of Epstein-Barr virus infected humans

The Epstein–Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is a virus of the herpes family, and is one of the most common viruses in humans. EBV infection, which occurs by oral transfer of the saliva, results in infectious mononucleosis (glandular fever). It is also associated with particular forms of cancer, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and central nervous system lymphomas associated with HIV. There is evidence that infection with the virus is associated with a higher risk of certain autoimmune diseases, especially dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis. Most people become infected with EBV and gain adaptive immunity. In the United States, about half of all five-year-old children and 90 to 95 percent of adults have evidence of previous infection. Infants become susceptible to EBV as soon as maternal antibody protection disappears. Many children become infected with EBV, and these infections usually cause no symptoms or are indistinguishable from the other mild, brief illnesses of childhood.

A mature EBV viral particle has a diameter of approximately 120 nm to 180 nm. It is composed of a double stranded, linear DNA genome enclosed by a protein capsid. The capsid is surrounded by a protein tegument, which in turn is surrounded by a lipid envelope. The EBV genome is about 192 thousand base pairs in length and contains about 85 genes. The viral envelope is embedded with glycoproteins essential to viral entry into the cell.

EBV Infection Cycle

EBV infects B cells of the immune system and epithelial cells. Once EBV enters the cell, the viral capsid dissolves and the viral genome is transported to the cell nucleus. An EBV infection can be described as being in one of two cycles; a lytic replicative cycle and a latency cycle.

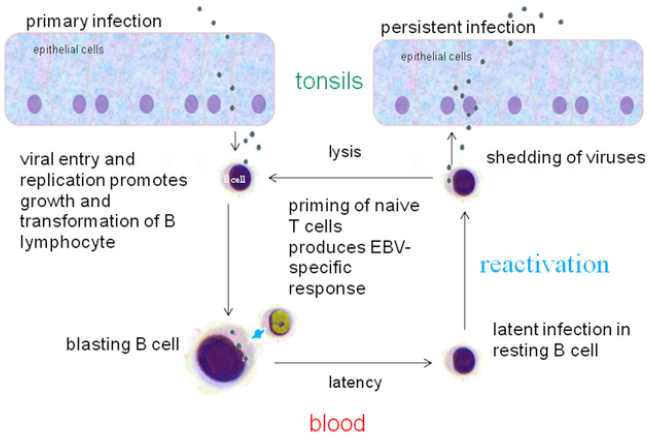

Figure: **EBV infection cycle**: Upon a primary infection, EBV enters the lytic replicative cycle where it infects blood cells. It will remain dormant during the latent stage until it is reactivated into the lytic cycle.

The lytic cycle, or productive infection, results in the production of infectious virions. EBV can undergo lytic replication in both B cells and epithelial cells. In B cells, lytic replication normally only takes place after reactivation from latency. In epithelial cells, lytic replication often directly follows viral entry entry. For lytic replication to occur, the viral genome must be linear. The latent EBV genome is circular, so it must linearize in the process of lytic reactivation. During lytic replication, viral DNA polymerase is responsible for copying the viral genome. Unlike lytic replication for many other viruses, EBV lytic replication does not inevitably lead to lysis of the host cell because EBV virions are produced by budding from the infected cell.

Unlike lytic replication, the latent stage does not result in production of virions. Instead, the EBV genome circularizes, resides in the cell nucleus as an episome, and is copied by cellular DNA polymerase. In latency, only a portion of EBV's genes are expressed. Latent EBV expresses its genes in one of three patterns, known as latency programs. EBV can latently persist within B cells and epithelial cells, but different latency programs are possible in the two types of cells. EBV can exhibit one of three latency

programs: Latency I, Latency II, or Latency III. Each latency program leads to the production of a limited, distinct set of viral proteins and viral RNAs.

Presence and Symptoms of EBV

The EBV occurs all over the world and most people become infected with this virus at some point in their lives. When teenagers get EBV, there is a 35-50% chance that it will lead to infectious mononucleosis also known as mono. Symptoms of mono include fever, sore throat, pharyngitis, and swollen lymph glands (lymphadenopathy). Although the symptoms of infectious mononucleosis usually go away in 1-2 months, EBV remails dormant and hidden in the troat and blood cells for the rest of the person's life.

Key Points

- The Epstein–Barr virus (EBV), is a very common virus and infects about 95% of all people in the United States.
- EBV can result in fever, sore throat, pharyngitis, and lymphadenopathy. Together, these symptoms are called infectious mononucleosis.
- An EBV infection can occur in two forms; a lytic replicative stage where it replicates its viral genome and produces gene products to help the virus evade the immune system and a latent stage where it remains undetected until reactivation.

Key Terms

- **epithelial cells**: cells that are part of the membranous tissue which form the covering of most internal and external surfaces of the body and its organs; internally including the lining of vessels and other small cavities, and externally being the skin.
- **lytic cycle**: The normal process of viral reproduction involving penetration of the cell membrane, nucleic acid synthesis, and lysis of the host cell.
- **B cell**: a lymphocyte, developed in the bursa of birds and the bone marrow of other animals, that produces antibodies and is responsible for the immune system.

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15.9D: Cytomegalovirus Infections

Cytomegalovirus (CMV) is a type of herpesvirus that largely affects infants and the immunocompromised.

Learning Objectives

- Describe the route of transmission and risks associated with the human cytomegalovirus (HCMV)

Key Points

- Cytomegalovirus (CMV) is a viral genus of the viral family known as Herpesviridae or herpesviruses.
- CMV infections are frequently associated with the salivary glands
- HCMV is found throughout all geographic locations and socioeconomic groups, and infects between 50% and 80% of adults in the United States
- CMV is generally transmitted from infected people to others through direct contact with body fluids, such as urine, saliva, vaginal secretions, and semen.

Key Terms

- **immunocompromised**: Having an immune system that has been impaired by disease or treatment.
- **Seroprevalence**: Seroprevalence is the number of persons in a population who test positive for a specific disease based on serology (blood serum) specimens; often presented as a percent of the total specimens tested or as a proportion per 100,000 persons tested.
- **major histocompatibility complex**: MHC is a cell surface molecule that mediate interactions of immune cells with other leukocytes or body cells. MHC determines compatibility of donors for organ transplants as well as one's susceptibility to an autoimmune disease. In humans, MHC is also called human leukocyte antigen (HLA).

Cytomegalovirus (CMV) is a viral genus of the viral family known as Herpesviridae or herpesviruses. The species that infects humans is commonly known as human CMV (HCMV) or human herpesvirus-5 (HHV-5), and is the most studied of all cytomegaloviruses. All herpesviruses can stay latent for long durations. Although they may be found throughout the body, CMV infections are frequently associated with the salivary glands in humans and other mammals. Other CMV viruses are found in several mammal species, but species isolated from animals differ from HCMV in terms of genomic structure, and have not been reported to cause human disease.

HCMV is found throughout all geographic locations and socioeconomic groups, and infects between 50% and 80% of adults in the United States (40% worldwide) as indicated by the presence of antibodies in much of the general population. Seroprevalence is age-dependent: 58.9% of individuals aged 6 and older are infected with CMV while 90.8% of individuals aged 80 and older are positive for HCMV. HCMV is also the virus most frequently transmitted to a developing fetus. HCMV infection is more widespread in developing countries and in communities with lower socioeconomic status; it represents the most significant viral cause of birth defects in industrialized countries. Major areas of risk of infection include prenatal or postnatal infants and immunocompromised individuals, such as organ transplant recipients, persons with leukemia, or those infected with human immunodeficiency virus (HIV).

CMV is generally transmitted from infected people to others through direct contact with body fluids, such as urine, saliva, vaginal secretions, and semen. Although they may be found throughout the body, HCMV infections are frequently associated with the salivary glands. HCMV infection is typically unnoticed in healthy people, but can be life-threatening for the immunocompromised, such as HIV-infected persons, organ transplant recipients, or newborn infants.

CMV, like all herpesviruses, can stay latent for long durations of time. The initial introduction of CMV generally gives way to an extended period of infection during which there is no detectable clinical illness. Severe impairment of the body's immune system reactivates the virus from this dormant state. CMV persists in the host because the viral genome encodes multiple proteins that interfere with major histocompatibility complex (MHC) class I presentation of viral antigens. One viral protein blocks translocation of peptides into the lumen of the endoplasmic reticulum, while two other viral proteins cause degradation of MHC class I proteins before they reach the cell surface. In AIDS patients, CMV can cause loss of vision (cotton wool spots), pneumonia, and hepatitis. Transplant patients with CMV are also susceptible to pneumonia and hepatitis.

A vaccine against (CMV) is currently under investigation. Because CMV can cause congenital infection, considerable effort has been made towards the development of a vaccine, with particular emphasis on protection for pregnant women. There are currently

three licensed anti-HCMV drugs target the viral DNA polymerase, pUL54. Ganciclovir (GCV) acts as nucleoside analogue. Its antiviral activity requires phosphorylation by the HCMV protein kinase, pUL97. The second drug, Cidofovir (CDV), is a nucleotide analogue, which is already phosphorylated and thus active. Finally, Foscarnet (FOS) has a different mode of action. It directly inhibits polymerase function by blocking the pyrophosphate binding site of pUL54.

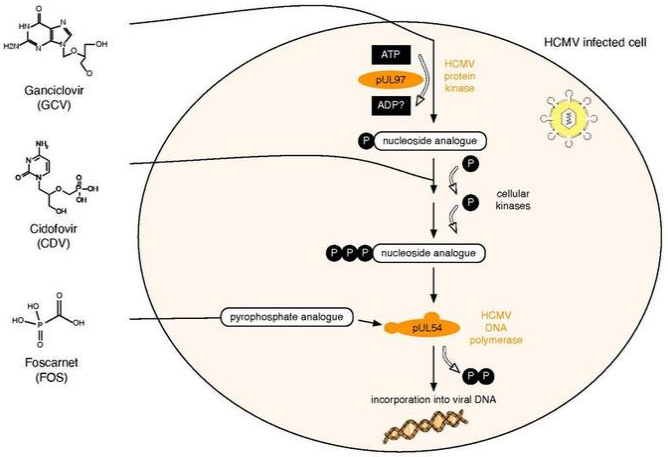

Figure: **HCMV drugs**: HCMV drugs have been designed to target the virus' DNA polymerase (pUL54), protein kinase (pUL97), and cellular kinases.

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15.9E: Chikungunya Fever

Chikungunya (CHIKV) is a mosquito-borne viral disease which causes fever and severe joint pain.

Learning Objectives

- Discuss the causes and symptoms associated with chikungunya virus (CHIKV)

Key Points

- The chikungunya virus is transmitted from human to human by the bites of infected female mosquitoes; the Aedes aegypti and Aedes albopictus mosquitoes.
- The disease occurs in Africa, Asia and the Indian subcontinent. In recent decades mosquito vectors of CHIKV have spread to Europe and the Americas.
- There is no cure for CHIKV. Treatment is focused on relieving the symptoms which include fever and severe joint pain, muscle pain, headache, nausea, fatigue and rash.

Key Terms

- **dengue**: An acute febrile disease of the tropics caused by a flavivirus, transmitted by mosquitoes, and characterized by high fever, rash, headache, and severe muscle and joint pain.
- **Aedes**: Aedes is a genus of mosquito originally found in tropical and subtropical zones, but now found on all continents excluding Antarctica.
- **chikungunya**: A viral fever caused by an alphavirus spread by mosquito bites.

Chikungunya Virus (CHIKV)

Chikungunya (in the Makonde language “that which bends up”) virus (CHIKV) is an insect-borne virus of the genus *Alphavirus*, that is transmitted to humans by virus-carrying *Aedes*(Ae) mosquitoes. Both *Ae. aegypti* and *Ae. albopictus* have been implicated in large outbreaks of CHIKV.

CHIKV infection causes an illness with symptoms similar to dengue fever, with an acute febrile phase of the illness lasting only two to five days, followed by a prolonged arthralgic disease that affects the joints of the extremities. The pain associated with CHIKV infection of the joints persists for weeks or months or, in some cases, years. CHIKV is indigenous to tropical Africa and Asia, where it is transmitted to humans by the bite of infected mosquitoes.



Figure: **Close up of Aedes aegypti mosquito**: The Aedes aegypti mosquito is the principle vector responsible for transmitting the chikungunya virus to humans.

SIGNS AND SYMPTOMS

The incubation period of chikungunya disease ranges from one to 12 days, but usually two to three. Its symptoms include a high fever up to 40 °C (104 °F), a petechial or maculopapular rash of the trunk and occasionally the limbs, and arthralgia or arthritis affecting multiple joints. Other nonspecific symptoms can include headache, conjunctivitis, slight photophobia and partial loss of taste. Typically, the fever lasts for two days and then ends abruptly. However, other symptoms—namely joint pain, intense headache, insomnia and an extreme degree of prostration—last for a variable period; usually for about five to seven days. Patients have complained of joint pains for much longer time periods; some for as long as two years, depending on their age.

DIAGNOSIS

Common laboratory tests for chikungunya include RT-PCR, virus isolation, and serological tests.

Virus isolation provides the most definitive diagnosis, but takes one to two weeks for completion and must be carried out in biosafety level-3 laboratories. The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses. RT-PCR using nested-primer pairs is used to amplify several chikungunya-specific genes from whole blood. Results can be determined in one to two days. Serological diagnosis requires a larger amount of blood than the other methods, and uses an ELISA assay to measure chikungunya-specific IgM levels. Results require two to three days.

TREATMENT

There are no specific drugs to cure the disease. Treatment is directed primarily at relieving the symptoms, especially the joint pain. There is no commercial chikungunya vaccine.

CHIKUNGUNYA OUTBREAKS

Chikungunya occurs in Africa, Asia, and the Indian subcontinent. Human infections in Africa have been at relatively low levels for a number of years, but in 1999-2000 there was a large outbreak in the Democratic Republic of the Congo, and in 2007 there was an outbreak in Gabon. Starting in February 2005, a major outbreak occurred in islands of the Indian Ocean. A large number of imported cases in Europe were associated with this outbreak, mostly in 2006 when this epidemic was at its peak.

A large outbreak of chikungunya in India occurred in 2006 and 2007. Several other countries in South-East Asia were also affected. In 2007 transmission was reported for the first time in Europe, in a localized outbreak in north-eastern Italy.

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15.9F: Classic Viral Hemorrhagic Fevers

Viral hemorrhagic fevers (VHFs) are a group of illnesses that are caused by several distinct families of RNA viruses.

Learning Objectives

- List the types, symptoms and routes of transmission for viral hemorrhagic fevers

Key Points

- VHFs are caused by viruses of four distinct families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses. They are all RNA viruses covered, or enveloped, in a fatty coating.
- Viruses associated with most VHFs naturally reside in an animal host or arthropod vector. For the most part, rodents and arthropods are the main reservoirs for viruses causing VHFs.
- Symptoms include marked fever, fatigue, dizziness, muscle aches, loss of strength, exhaustion, and excessive bleeding under the skin, in internal organs, or from body orifices like the mouth, eyes, or ears.

Key Terms

- **hemorrhagic**: of, relating to, or producing excessive loss of blood or blood escape from the circulatory system.

The viral hemorrhagic (or haemorrhagic) fevers (VHFs) are a diverse group of animal and human illnesses that may be caused by five distinct families of RNA viruses: the families Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae, and Rhabdoviridae. All types of VHF are characterized by fever and bleeding disorders and all can progress to high fever, shock and death in many cases. Some of the VHF agents cause relatively mild illnesses, such as the Scandinavian nephropathia epidemica, while others, such as the African Ebola virus, can cause severe, life-threatening disease.

Four families of RNA viruses have been recognized as causing this syndrome:

- The family Arenaviridae include the viruses responsible for Lassa fever, Lujo virus, Argentine, Bolivian, Brazilian and Venezuelan hemorrhagic fevers.
- The family Bunyaviridae include the members of the Hantavirus genus that cause hemorrhagic fever with renal syndrome (HFRS), the Crimean-Congo hemorrhagic fever (CCHF) virus from the Nairovirus genus, Garissa virus from the Orthobunyavirus and the Rift Valley fever (RVF) virus from the Phlebovirus genus.
- The family Filoviridae include Ebola virus and Marburg virus. Ebola has five viral subtypes including Zaire, Sudan, Bundibugyo, Tai Forest (formerly Ivory Coast), and Reston.
- The family Flaviviridae include dengue, yellow fever, and two viruses in the tick-borne encephalitis group that cause VHF: Omsk hemorrhagic fever virus and Kyasanur Forest disease virus.

Transmission

Transmission to humans depends on the specific virus, but includes:

- By contact with the urine, feces, saliva, or blood of animal hosts such as rodents, fruit bats, subhuman primates, and duikers (antelope)
- From mosquito or tick bites
- Contact with vector-infected livestock
- Consuming infected bush meat

Signs and Symptoms

Signs and symptoms of VHFs include fever and bleeding diathesis. Manifestations of VHF often also include flushing of the face and chest, petechiae, frank bleeding, edema, hypotension, and shock. Malaise, myalgias, headache, vomiting, and diarrhea occur frequently. Definitive diagnosis is usually made at a reference laboratory with advanced biocontainment capabilities.

Treatment

For most viral hemorrhagic fevers, there is no effective treatment other than supportive care. The only licensed vaccine available is for yellow fever. Control of rodent populations, insect and other arthropod populations can prevent VHFs.

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15.9G: Emerging Viral Hemorrhagic Fevers

As human habitation expands, new viral hemorrhagic fevers are infecting humans.

Learning Objectives

- Generalize the characteristics and implications of an emergent virus

Key Points

- There are several types of viruses that cause hemorrhagic fevers they are typified by high fever and bleeding.
- Emergent viruses are newly discovered viruses, often coming from other animal species. Many emergent viruses are uncovered by human activity such as deforestation.
- New sequencing technologies allow the identification of emergent viruses.
- No other rhabdovirus is known to cause the acute, rapid and deadly hemorrhagic fever seen in the three cases in the Congo.

Key Terms

- **Rhabdovirus**: Rhabdoviruses are viruses belonging to the family Rhabdoviridae,that infect a broad range of hosts throughout the animal and plant kingdoms.

An emergent virus is a virus that has adapted and emerged as a new disease/pathogenic strain, with attributes facilitating pathogenicity in a field not normally associated with that virus. This includes viruses that are the cause of a disease that has notably increased in incidence; this is often a result of a wide variety of causes from both the influence of man and nature. Most emergent viruses can be categorized as zoonotic; an animal disease that can be transmitted to humans. The virus thus has the advantage of possibly having several natural reservoirs to propagate in. As human development increases, and we move into areas not previously inhabited a reservoir of a virus can be uncovered and infections of humans ensues. This is especially worse in tropical areas of the world with high levels of biodiversity such as Africa, South America, and South Asia. Many newly discovered viruses come from these parts of the world as human habitation expands.

The viral hemorrhagic fevers (VHFs) are a diverse group of animal and human illnesses that may be caused by five distinct families of RNA viruses: the families Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae, and Rhabdoviridae. All types of VHF are characterized by fever and bleeding disorders and all can progress to high fever, shock and death in many cases. Some of the VHF agents cause relatively mild illnesses, such as the Scandinavian nephropathia epidemica, while others, such as the African Ebola virus, can cause severe, life-threatening disease.

Indeed the advent of deep sequencing technologies and other methods are identifying emergent viral hemorrhagic fevers. A recent study using deep sequencing, discovered a novel rhabdovirus (Bas-Congo virus, or BASV) associated with a 2009 outbreak of three human cases of acute hemorrhagic fever in Mangala village, Democratic Republic of Congo (DRC), Africa. The cases, presenting over a three-week period, were characterized by abrupt disease onset, high fever, bloody vomiting, and diarrhea, and, in two patients, death within three days. BASV was present in the blood of the lone survivor at a concentration of over a million copies per milliliter. The genome of BASV, assembled from over 140 million sequence reads, reveals that it is very different from any other rhabdovirus. The lone survivor and a nurse caring for him (with no symptoms), both health care workers, were found to have high levels of antibodies to BASV, indicating that they both had been infected by the virus. Although the source of the virus remains unclear, the study findings suggest that BASV may be spread by human-to-human contact and is an emerging pathogen associated with acute hemorrhagic fever in Africa.

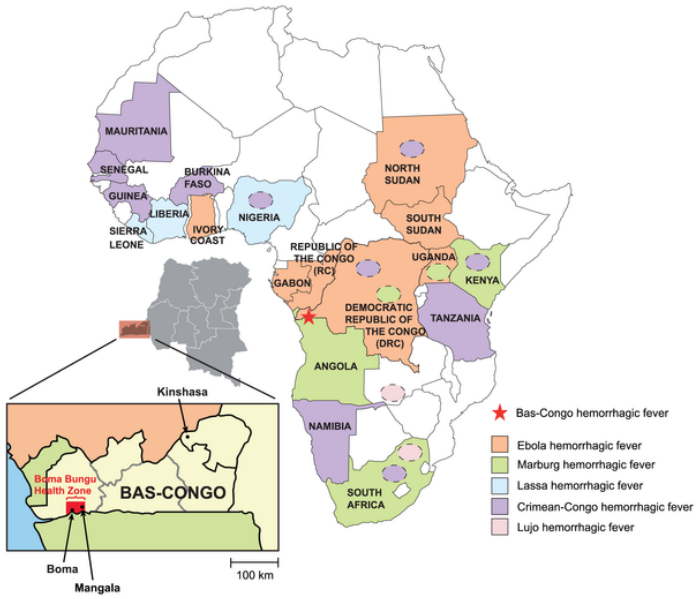

Figure: **Countries affected by viral hemorrhagic fever (VHF) outbreaks**: Mangala village, located in the Bas-Congo province in DRC, is represented by a red star.

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***Thumbnail**: Hydrothermal vents are cracks in the earth's crust where geothermally heated water leaks out.*

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SECTION OVERVIEW

16.1: Microbial Ecology

Topic hierarchy

16.1A: Microbes and Ecosystem Niches

16.1B: Organization of Ecosystems

16.1C: Role of Microbes in Biogeochemical Cycling

16.1D: Microbial Environments and Microenvironments

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16.1A: Microbes and Ecosystem Niches

Every ecosystem on Earth contains microorganisms that occupy unique niches based on their specific metabolic properties.

Learning Objectives

- Evaluate microbes and the niches they occupy

Key Points

- Microbes live in all parts of the biosphere where there is liquid water.
- By virtue of their omnipresence, microbes impact the entire biosphere.
- Each microbial species in an ecosystem is thought to occupy a unique niche, which is a complex description of the ways in which an organism uses its environment.
- The precise ecological niche of a microbe is primarily determined by the specific metabolic properties of that organism.

Key Terms

- **bioremediation**: The use of biological organisms, usually microorganisms, to remove contaminants, especially from polluted water.
- **niche**: A function within an ecological system to which an organism is especially suited.
- **biosphere**: The part of the Earth and its atmosphere capable of supporting life.

Microbes and Ecosystem Niches

Microbial life is amazingly diverse and microorganisms quite literally cover the planet. In fact, it has been estimated that there are 100,000,000 times more microbial cells on the planet than there are stars in the observable universe! Microbes live in all parts of the biosphere where there is liquid water, including soil, hot springs, the ocean floor, acid lakes, deserts, geysers, rocks, and even the mammalian gut.

By virtue of their omnipresence, microbes impact the entire biosphere; indeed, microbial metabolic processes (including nitrogen fixation, methane metabolism, and sulfur metabolism) collectively control global biogeochemical cycling. The ability of microbes to contribute substantially to the function of every ecosystem is a reflection their tremendous biological diversity.



Figure: **A Biofilm of Thermophilic Bacteria**: Thermophiles, which thrive at relatively high temperatures, occupy a unique ecological niche. This image shows a colony of thermophilic bacteria at Mickey Hot Springs in Oregon, USA.

Microbes are vital to every ecosystem on Earth and are particularly important in zones where light cannot approach (that is, where photosynthesis cannot be the basic means to collect energy). Microorganisms participate in a host of fundamental ecological processes including production, decomposition, and fixation. They can also have additional indirect effects on the ecosystem through symbiotic relationships with other organisms. In addition, microbial processes can be co-opted for biodegradation or bioremediation of domestic, agricultural, and industrial wastes, making the study of microbial ecology particularly important for biotechnological and environmental applications.

Each species in an ecosystem is thought to occupy a separate, unique niche. The ecological niche of a microorganism describes how it responds to the distribution of resources and competing species, as well as the ways in which it alters those same factors in turn. In essence, the niche is a complex description of the ways in which a microbial species uses its environment.

The precise ecological niche of a microbe is primarily determined by the specific metabolic properties of that organism. For example, microbial organisms that can obtain energy from the oxidation of inorganic compounds (such as iron-reducing bacteria) will likely occupy a different niche from those that obtain energy from light (such as cyanobacteria). Even among photosynthetic bacteria, there are various species that contain different photosynthetic pigments (such as chlorophylls and carotenoids) that allow

them to take advantage of different portions of the electromagnetic spectrum; therefore, even microbes with similar metabolic properties may inhabit unique niches.

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16.1B: Organization of Ecosystems

Microorganisms serve essential roles in the complex nutrient exchange system that defines an ecological community.

Learning Objectives

- Illustrate the organization of ecosystems

Key Points

- An ecosystem is a unified system of exchange made up of autotrophic producers, heterotrophic consumers, and decomposers.
- A food web depicts a collection of heterotrophic consumers that network and cycle the flow of energy and nutrients from a productive base of self-feeding autotrophs.
- Microorganisms play a vital role in every ecological community by serving as both producers and decomposers.

Key Terms

- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **heterotroph**: An organism that requires an external supply of energy in the form of food as it cannot synthesize its own.

Although ecologists tend to regard ecosystems as basic structural units, it can be difficult (if not impossible) to formally define the boundaries of a given ecosystem. As such, ecosystems are better thought of as *conceptual* rather than *actual* geographical locations. Rarely are ecosystems isolated from one another; rather, they should be considered parts of a larger functioning whole that together comprise the biosphere ("the place on Earth's surface where life dwells").

Despite the fact that clear boundaries between ecosystems may be difficult to identify, the myriad interactions that take place *within* an ecological community can often be observed and defined. These interactions may be best described by detailing feeding connections (what eats what) among biota in an ecosystem, thereby linking the ecosystem into a unified system of exchange.

All life forms in an ecosystem can be broadly grouped into one of two categories (called trophic levels):

- Autotrophs, which produce organic matter (food) from inorganic substances; and
- Heterotrophs, which must feed on other organisms in order to obtain organic matter.

In general, trophic levels are used to describe the way in which a particular organism within an ecosystem gets its food. Using this description, we can restate and reorganize the categories above to define the three basic ways organisms acquire their food:

- Producers (autotrophs) do not usually eat other organisms but pull nutrients from the soil or the ocean and manufacture their own food using photosynthesis. In this way, it is the energy from the sun that usually powers the base of the food chain.
- Consumers (heterotrophs) cannot manufacture their own food and need to consume other organisms.
- Decomposers break down dead plant and animal material and wastes and release them into the ecosystem as energy and nutrients for recycling.

Within ecosystems, the biotic factors that comprise the categories above can be organized into a food chain in which autotrophic producers use materials and nutrients recycled by decomposers to make their own food; the producers are in turn eaten by heterotrophic consumers. In real world ecosystems, there are multiple food chains for most organisms (since most organisms eat more than one kind of food or are eaten by more than one type of predator). Additionally, the movement of mineral nutrients in the food chain is cyclic rather than linear. As a consequence, the intricate network of intersecting and overlapping food chains for an ecosystem is more commonly represented as a food web. A food web depicts a collection of heterotrophic consumers that network and cycle the flow of energy and nutrients from a productive base of self-feeding autotrophs.

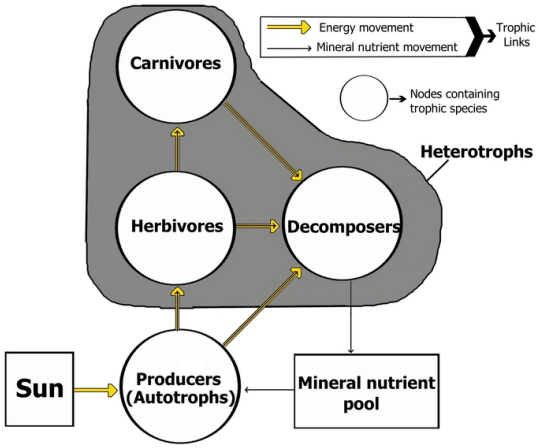

Figure: **A simplified food web**: This image shows a simplified food web model of energy and mineral nutrient movement in an ecosystem. Energy flow is unidirectional (noncyclic) and mineral nutrient movement is cyclic.

Microorganisms play a vital role in every ecological community by serving both as producers and as decomposers. Although plants are the most common primary producers, autotrophic photosynthetic microbes (such as cyanobacteria and algae) can harness light energy to generate organic matter. Additionally, in zones where light cannot penetrate (and thus photosynthesis cannot be the basic means to produce energy), chemosynthetic microbes provide energy and carbon to the other organisms in the ecosystem. Other microbes are decomposers, with the ability to recycle nutrients from dead organic matter and other organisms' waste products. Decomposition is critical as most of the carbon and energy incorporated into plant tissues during photosynthesis remains uneaten when the plant tissue dies (and therefore must be broken down before it can be made available for recycling).

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16.1C: Role of Microbes in Biogeochemical Cycling

Microbes form the backbone of every ecological system by controlling global biogeochemical cycling of elements essential for life.

Learning Objectives

- Explain the role microbes play in biogeochemical cycling

Key Points

- A biogeochemical cycle is a pathway by which a chemical element (such as carbon or nitrogen) circulates through and is recycled by an ecosystem.
- Microorganisms play a primary role in regulating biogeochemical systems in virtually all of our planet ‘s environments.
- Microbes participate in essential biogeochemical cycling events such as carbon and nitrogen fixation.

Key Terms

- **photosynthesis**: The process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts.
- **biogeochemistry**: The scientific study of biological, geological, and chemical processes in the natural environment and especially of their mutual relationships.
- **nitrogenase**: The enzyme, in nitrogen-fixing bacteria, that catalyzes the conversion of atmospheric nitrogen into ammonia.

Microbial Role in Biogeochemical Cycling

Nutrients move through the ecosystem in biogeochemical cycles. A biogeochemical cycle is a pathway by which a chemical element (such as carbon or nitrogen) circulates through the biotic (living) and the abiotic (non-living) factors of an ecosystem. The elements that move through the factors of an ecosystem are not lost but are instead recycled or accumulated in places called reservoirs (or “sinks”) where they can be held for a long period of time. Elements, chemical compounds, and other forms of matter are passed from one organism to another and from one part of the biosphere to another through these biogeochemical cycles.

Ecosystems have many biogeochemical cycles operating as a part of the system. A good example of a molecule that is cycled within an ecosystem is water, which is always recycled through the water cycle. Water undergoes evaporation, condensation, and then falls back to Earth as rain (or other forms of precipitation). This typifies the cycling that is observed for all of the principal elements of life.

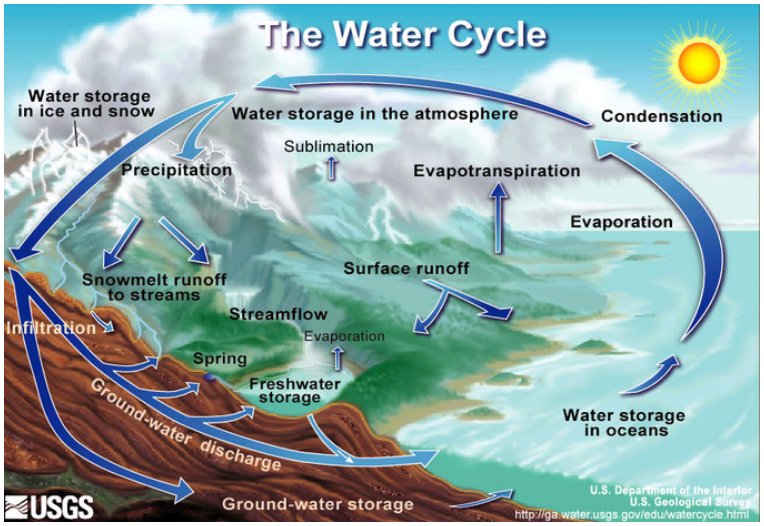

Figure: **The Water Cycle**: Water is recycled in an ecosystem through the water cycle.

Although biogeochemical cycles in a given ecosystem are coordinated by the full complement of living organisms and abiotic factors that make up that system, microorganisms play a primary role in regulating biogeochemical systems in virtually all of our planet’s environments. This includes extreme environments such as acid lakes and hydrothermal vents, and even includes living systems such as the human gut. The key collective metabolic processes of microbes (including nitrogen fixation, carbon fixation,

methane metabolism, and sulfur metabolism) effectively control global biogeochemical cycling. Incredibly, production by microbes is so immense that global biogeochemistry would likely not change even if eukaryotic life were totally absent!

Microbes comprise the backbone of every ecological system, particularly those in which there is no light (i.e. systems in which energy cannot be collected through photosynthesis). Two key examples of critical biogeochemical processes carried out by microorganisms are discussed below.

The Carbon Cycle

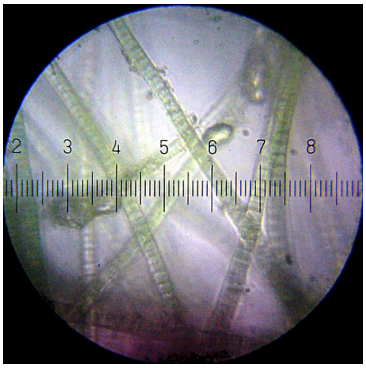

Figure: **Cyanobacteria**: Cyanobacteria, also known as blue-green bacteria, blue-green algae, and Cyanophyta, is a phylum of bacteria that obtain their energy through photosynthesis

Carbon is critical for life because it is the essential building block of all organic compounds. Plants and animals utilize carbon to produce carbohydrates, fats, and proteins, which can then be used to build their internal structures or to obtain energy.

Carbon in the form of carbon dioxide (CO_2) is readily obtained from the atmosphere, but before it can be incorporated into living organisms it must be transformed into a usable organic form. The transformative process by which carbon dioxide is taken up from the atmospheric reservoir and “fixed” into organic substances is called carbon fixation. Perhaps the best known example of carbon fixation is photosynthesis, a process by which energy derived from sunlight is harnessed to form organic compounds. Photosynthesis depends on the activity of microorganisms such as cyanobacteria; indeed, the fact that there is oxygen in the Earth’s atmosphere at all is a consequence of the photosynthetic activity of ancient microbes.

The Nitrogen Cycle

Nitrogen is essential for all forms of life because it is required for synthesis of the basic building blocks of life (e.g., DNA, RNA, and amino acids). The Earth’s atmosphere is primarily composed of nitrogen, but atmospheric nitrogen (N_2) is relatively unusable for biological organisms. Consequently, chemical processing of nitrogen (or nitrogen fixation) is necessary to convert gaseous nitrogen into forms that living organisms can use. Almost all of the nitrogen fixation that occurs on the planet is carried out by bacteria that have the enzyme nitrogenase, which combines N_2 with hydrogen to produce a useful form of nitrogen (such as ammonia). Thus, microorganisms are absolutely essential for plant and animal life forms, which cannot fix nitrogen on their own.

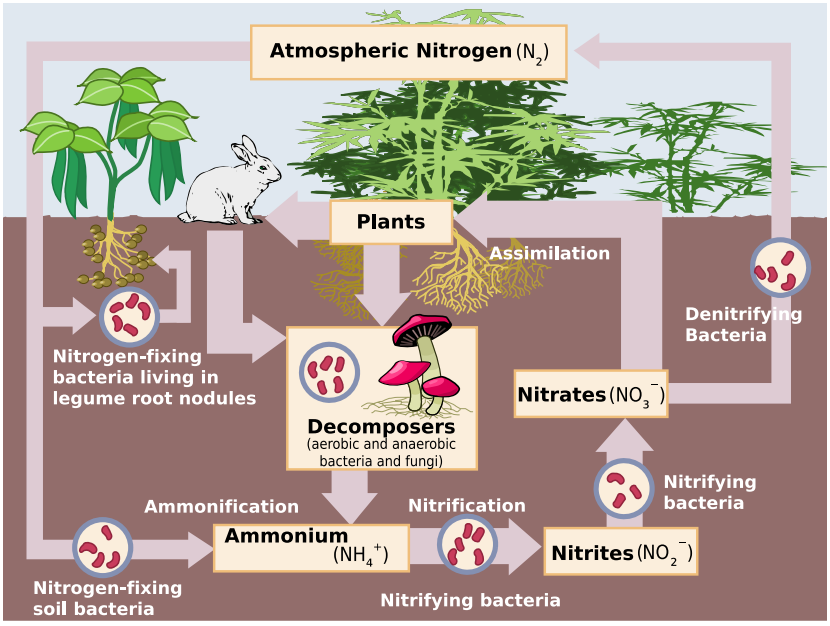

Figure: **The Role of Microbes in the Nitrogen Cycle**: The processing of nitrogen into a biologically useful form requires the activity of microorganisms.

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16.1D: Microbial Environments and Microenvironments

The extraordinary biological diversity among microbes reflects their ability to occupy every habitable environment on the planet.

Learning Objectives

- Define microenvironments

Key Points

- Microorganisms are found in practically every habitat present on the planet.
- Microorganisms have evolved to survive in extraordinarily diverse environments, including extreme, hostile, or otherwise intolerant ecological systems.
- In addition to occupying a unique niche within an ecosystem, microbes adapt to microenvironments (or microhabitats) that can be distinguished from the immediate surroundings by such factors as the amount of incident light, the degree of moisture, and the range of temperatures.

Key Terms

- **microenvironment**: The very small environment in the immediate vicinity of an organism.
- **extremophilic**: Of or pertaining to the extremophiles, a class of organism that thrives under extreme conditions of temperature, salinity, and so on; commercially important as a source of enzymes that operate under similar conditions.
- **ubiquitous**: Being everywhere at once: omnipresent.

Microorganisms are found on practically every habitable square inch of the planet. They live and thrive in all parts of the biosphere where there is liquid water, including hostile environments such as the poles, deserts, geysers, rocks, and the deep sea. Additionally, while microbes are often free-living, many have intimate symbiotic relationships with other larger organisms. Clearly, microbes have adapted to extreme and intolerant conditions, and it is this adaptation that has yielded tremendous biological diversity among microorganisms.

Like all extant organisms, microbes have evolved to thrive within a given environmental context. Microorganisms are ubiquitous despite the fact that the planet is host to extraordinarily diverse environments. Therefore, microbes have adapted to fill every ecological niche on the planet. For example, extremophilic species have been found that can tolerate the following environmental extremes:

- Temperatures as high as 130 °C (266 °F) and as low as −17 °C (1 °F)
- Highly alkaline (pH 0) and highly acidic (pH 11.5) environments
- Extremely saline environments (including those in which the salt concentration is saturating)
- Extremely high (1,000-2,000 atm) and low (0 atm) pressures (some bacteria can survive for prolonged periods in a pressure-less vacuum, meaning they might even survive in space)
- High ionizing radiation (up to 15,000 Gy; as a reference, a mere 5 Gy would kill a human!)

These evolutionary adaptations have allowed microbial life to extend into much of the Earth's atmosphere, crust, and hydrosphere (the water found over, under, and on the surface of a planet).

In addition to occupying a unique niche within an ecosystem, microbes are potentially sensitive to subtle environmental differences between adjacent areas. These differences define so-called microenvironments (or microhabitats) that can be distinguished from the immediate surroundings by such factors as the amount of incident light, the degree of moisture, and the range of temperatures. For example, the side of a tree that is shaded from sunlight is a microenvironment that typically supports a somewhat different community of microorganisms than would be found on the side that receives regular light. Microbes, therefore, are not only adapted to their habitat, but also to the immediate environment, thus promoting increased diversity among microbial species within an ecosystem.

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SECTION OVERVIEW

16.2: Soil and Plant Microbiology

Topic hierarchy

16.2A: Soil Composition

16.2B: Physical Properties of Soil

16.2C: Mycorrhiza

16.2D: Wetland Soils

16.2E: Endophytes and Plants

16.2F: Mycorrhizae: The Symbiotic Relationship between Fungi and Roots

16.2F: Plant Pathogens

16.2G: Nitrogen Fixation: Root and Bacteria Interactions

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16.2A: Soil Composition

Learning Objectives

- Explain soil composition

Plants obtain inorganic elements from the soil, which serves as a natural medium for land plants. Soil is the outer, loose layer that covers the surface of Earth. Soil quality, a major determinant, along with climate, of plant distribution and growth, depends not only on the chemical composition of the soil, but also the topography (regional surface features) and the presence of living organisms.

Soil consists of these major components:

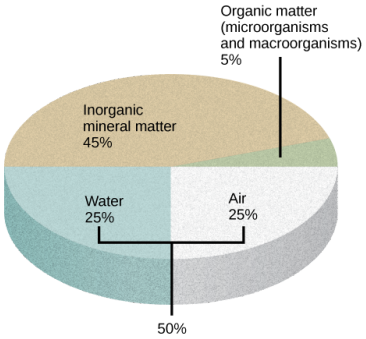

Figure: **Components of soil**: The four major components of soil are shown: inorganic minerals, organic matter, water, and air.

- inorganic mineral matter, about 40 to 45 percent of the soil volume
- organic matter, about 5 percent of the soil volume
- water, about 25 percent of the soil volume
- air, about 25 percent of the soil volume

The amount of each of the four major components of soil depends on the quantity of vegetation, soil compaction, and water present in the soil. A good, healthy soil has sufficient air, water, minerals, and organic material to promote and sustain plant life.

The organic material of soil, called humus, is made up of microorganisms (dead and alive), and dead animals and plants in varying stages of decay. Humus improves soil structure, providing plants with water and minerals. The inorganic material of soil is composed of rock, slowly broken down into smaller particles that vary in size. Soil particles that are 0.1 to 2 mm in diameter are sand. Soil particles between 0.002 and 0.1 mm are called silt, and even smaller particles, less than 0.002 mm in diameter, are called clay. Some soils have no dominant particle size, containing a mixture of sand, silt, and humus; these soils are called **loams**.

Key Points

- The chemical composition of the soil, the topography, and the presence of living organisms determines the quality of soil.
- In general, soil contains 40-45% inorganic matter, 5% organic matter, 25% water, and 25% air.
- In order to sustain plant life, the proper mix of air, water, minerals, and organic material is required.
- Humus, the organic material in soil, is composed of microorganisms (dead and alive) and decaying plants.
- The inorganic material of soil is composed of rock, which is broken down into small particles of sand (0.1 to 2 mm), silt (0.002 to 0.1 mm), and clay (less than 0.002 mm).
- Loam is a soil that is a mix sand, silt, and humus.

Key Terms

- **loam**: soil with no dominant particle size that contains a mixture of sand, silt, and humus
- **humus**: a large group of natural organic compounds found in the soil composed of decaying plants and dead and living microorganisms

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16.2B: Physical Properties of Soil

Learning Objectives

- Describe the physical properties or profile of soil

Soils are named and classified based on their horizons. The soil profile has four distinct layers:

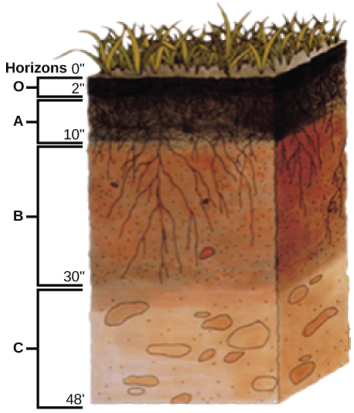

Figure: **Soil profile**: This soil profile shows the different soil layers (O horizon, A horizon, B horizon, and C horizon) found in typical soils.

1. The O horizon has freshly-decomposing organic matter, humus, at its surface, with decomposed vegetation at its base. Humus enriches the soil with nutrients, enhancing soil moisture retention. Topsoil, the top layer of soil, is usually two to three inches deep, but this depth can vary considerably. For instance, river deltas, such as the Mississippi River delta, have deep layers of topsoil. Topsoil is rich in organic material. Microbial processes occur there; it is responsible for plant production.
2. The A horizon consists of a mixture of organic material with inorganic products of weathering; it is the beginning of true mineral soil. This horizon is typically darkly colored because of the presence of organic matter. In this area, rainwater percolates through the soil and carries materials from the surface.
3. The B horizon, or subsoil, is an accumulation of mostly fine material that has moved downward, resulting in a dense layer in the soil. In some soils, the B horizon contains nodules or a layer of calcium carbonate.
4. The C horizon, or soil base, includes the parent material, plus the organic and inorganic material that is broken down to form soil. The parent material may be either created in its natural place or transported from elsewhere to its present location. Beneath the C horizon lies bedrock.

Some soils may have additional layers, or lack one of these layers. The thickness of the layers is also variable, depending on the factors that influence soil formation. In general, immature soils may have O, A, and C horizons, whereas mature soils may display all of these, plus additional layers.

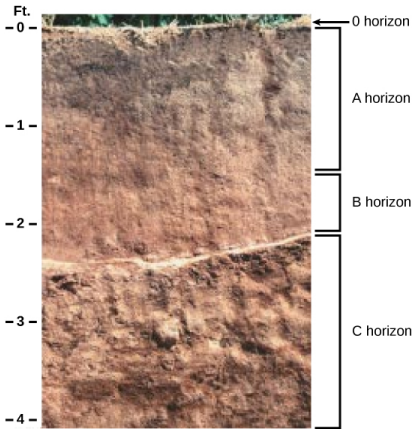

Figure: **Mature soil**: The San Joaquin soil is a mature soil that has an O horizon, A horizon, B horizon, and C horizon.

Key Points

- The O horizon, or topsoil, is made of decaying organisms and plant life; it is responsible for plant production.
- The A horizon is of a mixture of organic material and inorganic products of weathering; it is the beginning of true mineral soil.
- The B horizon, or subsoil, is a dense layer of mostly fine material that has been pushed down from the topsoil.
- The C horizon, or soil base, is located just above bedrock and is made of parent, organic, and inorganic material.

Key Terms

- **topsoil**: top layer of soil containing humus at its surface and decomposing vegetation at its base; the most fertile soil
- **subsoil**: dense layer of soil containing fine material that has moved downward; the layer of earth that is below the topsoil

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16.2C: Mycorrhiza

A mycorrhiza is a symbiotic association between a fungus and the roots of a vascular plant.

Learning Objectives

- Evaluate mycorrhiza as a plant symbiote

Key Points

- In a mycorrhizal association, the fungus colonizes the host plant's roots, either intracellularly as in arbuscular mycorrhizal fungi (AMF or AM) or extracellularly as in ectomycorrhizal fungi.
- Mycorrhiza are named after their presence in the plant's rhizosphere (root system). This mutualistic association provides the fungus with relatively constant and direct access to carbohydrates, such as glucose and sucrose.
- Plants grown in sterile soils and growth media often perform poorly without the addition of spores or hyphae of mycorrhizal fungi to colonize the plant roots and aid in the uptake of soil mineral nutrients.

Key Terms

- **mycorrhiza**: A symbiotic relationship between the mycelium of a fungus and the roots of a plant.

A mycorrhiza is a symbiotic (generally mutualistic, but occasionally weakly pathogenic) association between a fungus and the roots of a vascular plant.

In a mycorrhizal association, the fungus colonizes the host plant's roots, either intracellularly as in arbuscular mycorrhizal fungi (AMF or AM) or extracellularly as in ectomycorrhizal fungi. They are an important component of soil life and soil chemistry. Mycorrhizas form a mutualistic relationship with the roots of most plant species. While only a small proportion of all species has been examined, 95% of those plant families are predominantly mycorrhizal.

They are named after their presence in the plant's rhizosphere (root system). This mutualistic association provides the fungus with relatively constant and direct access to carbohydrates, such as glucose and sucrose. The carbohydrates are translocated from their source (usually leaves) to root tissue and on to the plant's fungal partners. In return, the plant gains the benefits of the mycelium's higher absorptive capacity for water and mineral nutrients due to the comparatively large surface area of mycelium: root ratio, thus improving the plant's mineral absorption capabilities. Plant roots alone may be incapable of taking up phosphate ions that are demineralized in soils with a basic pH. The mycelium of the mycorrhizal fungus can, however, access these phosphorus sources and make them available to the plants they colonize.

Suillus tomentosus, a fungus, produces specialized structures, known as tuberculate ectomycorrhizae, with its plant host lodgepole pine (Pinus contorta var. latifolia). These structures have in turn been shown to host nitrogen fixing bacteria which contribute a significant amount of nitrogen and allow the pines to colonize nutrient-poor sites.

Plants grown in sterile soils and growth media often perform poorly without the addition of spores or hyphae of mycorrhizal fungi to colonize the plant roots and aid in the uptake of soil mineral nutrients.

Fungi have been found to have a protective role for plants rooted in soils with high metal concentrations, such as acidic and contaminated soils. Pine trees inoculated with Pisolithus tinctorius planted in several contaminated sites displayed high tolerance to the prevailing contaminant, survivorship, and growth.

Mycorrhizas are present in 92% of plant families studied (80% of species), with arbuscular mycorrhizas being the ancestral and predominant form and the most prevalent symbiotic association found in the plant kingdom. The structure of arbuscular mycorrhizas has been highly conserved since their first appearance in the fossil record.

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16.2D: Wetland Soils

Wetlands are considered one of the most biologically diverse of all ecosystems.

Learning Objectives

- Assess the composition of wetland soils

Key Points

- Nutrient cycling in lakes and freshwater wetlands depends heavily on redox conditions.
- Some anaerobic microbial processes include denitrification, sulfate reduction and methanogenesis and are responsible for the release of N2 (nitrogen), H2S (hydrogen sulfide) and CH4 (methane).
- Other anaerobic microbial processes are linked to changes in the oxidation state of iron and manganese and as a result of anaerobic decomposition, the soil stores large amounts of organic carbon because decomposition is incomplete.

Key Terms

- **denitrification**: The process by which a nitrate becomes molecular nitrogen, especially by the action of bacteria.
- **methanogenesis**: The generation of methane by anaerobic bacteria.
- **heterotroph**: An organism that requires an external supply of energy in the form of food as it cannot synthesize its own.

A wetland is a land area that is saturated with water, either permanently or seasonally, such that it takes on the characteristics of a distinct ecosystem. Primarily, the factor that distinguishes wetlands from other land forms or water bodies is the characteristic vegetation that is adapted to its unique soil conditions: Wetlands consist primarily of hydric soil, which supports aquatic plants. The water found in wetlands can be saltwater, freshwater, or brackish. Main wetland types include swamps, marshes, bogs and fens. Sub-types include mangrove, carr, pocosin, and varzea.

Wetlands play a number of roles in the environment, principally water purification, flood control, and shoreline stability. Wetlands are also considered the most biologically diverse of all ecosystems, serving as home to a wide range of plant and animal life.

In balanced soil, plants grow in an active and steady environment. The mineral content of the soil and its heartiful structure are important for their well-being, but it is the life in the earth that powers its cycles and provides its fertility. Without the activities of soil organisms, organic materials would accumulate and litter the soil surface, and there would be no food for plants.

The soil biota includes:

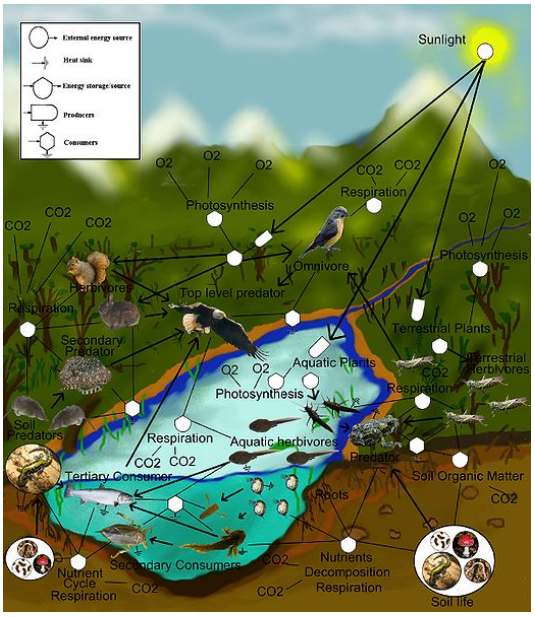

Figure: **A freshwater aquatic and terrestrial food-web.**: The food web is a complex and interconnected.

Megafauna: size range – 20 mm upward, e.g. moles, rabbits, and rodents.

Mesofauna: size range – 100 micrometres to 2 mm, e.g. tardigrades, mites, and springtails.

Microfauna and Microflora: size range – 1 to 100 micrometres, e.g. yeasts, bacteria (commonly actinobacteria), fungi, protozoa, roundworms, and rotifers.

Of these, bacteria and fungi play key roles in maintaining a healthy soil. They act as decomposers that break down organic materials to produce detritus and other breakdown products. Soil detritivores, like earthworms, ingest detritus and decompose it. Saprotrophs, well represented by fungi and bacteria, extract soluble nutrients from delitro. The ants (macrofaunas) help by breaking down in the same way but they also provide the motion part as they move in their armies. Also the rodents, wood-eaters help the soil to be more absorbent.

Nutrient cycling in lakes and freshwater wetlands depends heavily on redox conditions. Under a few millimeters of water heterotrophic bacteria metabolize and consume oxygen. They therefore deplete the soil of oxygen and create the need for anaerobic respiration. Some anaerobic microbial processes include denitrification, sulfate reduction and methanogenesis and are responsible for the release of N_2 (nitrogen), H_2S (hydrogen sulfide) and CH_4 (methane). Other anaerobic microbial processes are linked to changes in the oxidation state of iron and manganese. As a result of anaerobic decomposition, the soil stores large amounts of organic carbon because decomposition is incomplete.

The redox potential describes which way chemical reactions will proceed in oxygen deficient soils and controls the nutrient cycling in flooded systems. Redox potential, or reduction potential, is used to express the likelihood of an environment to receive electrons and therefore become reduced. For example, if a system already has plenty of electrons (anoxic, organic-rich shale) it is reduced and will likely donate electrons to a part of the system that has a low concentration of electrons, or an oxidized environment, to equilibrate to the chemical gradient. The oxidized environment has high redox potential, whereas the reduced environment has a low redox potential.

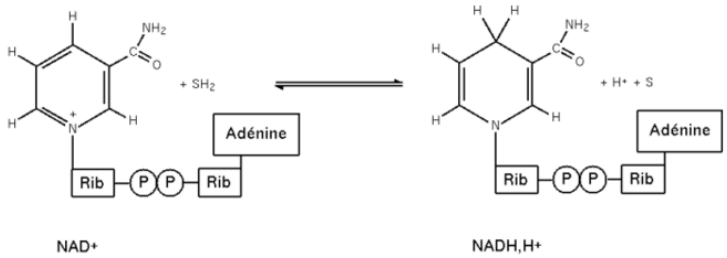

Figure: **Redox Potential**: The redox potential describes which way chemical reactions will proceed in oxygen deficient soils and controls the nutrient cycling in flooded systems.

The redox potential is controlled by the oxidation state of the chemical species, pH and the amount of oxygen (O_2) there is in the system. The oxidizing environment accepts electrons because of the presence of O_2, which acts as electron acceptors:

$$O_2 + 4e^- + 4H^+ \rightarrow H_2O$$

This equation will tend to move to the right in acidic conditions which causes higher redox potentials to be found at lower pH levels. Bacteria, heterotrophic organisms, consume oxygen while decomposing organic material which depletes the soils of oxygen, thus increasing the redox potential. In low redox conditions the deposition of ferrous iron (Fe^{2+}) will increase with decreasing decomposition rates, thus preserving organic remains and depositing humus.

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16.2E: Endophytes and Plants

An endophyte is an endosymbiont, often a bacterium or fungus, that lives within a plant for at least part of its life without causing apparent disease.

Learning Objectives

- Evaluate endophytes as plant pathogens

Key Points

- Endophytes are ubiquitous and have been found in all the species of plants studied to date.
- Vertically transmitted fungal endophytes are asexual and transmit via fungal hyphae penetrating the host ‘s seeds (e.g., Neotyphodium).
- The wide range of compounds produced by endophytes have been shown to combat pathogens and even cancers in animals including humans.

Key Terms

- **endophyte**: Any organism that lives inside another plant.

An endophyte is an endosymbiont, often a bacterium or fungus, that lives within a plant for at least part of its life without causing apparent disease. Endophytes are ubiquitous and have been found in all the species of plants studied to date. However, most of these endophyte/plant relationships are not well understood. Many economically important forage and turfgrasses (e.g., Festuca spp., Lolium spp.) carry fungal endophytes (Neotyphodium spp.) which may improve the ability of these grasses to tolerate abiotic stresses such as drought, as well as improve their resistance to insect and mammalian herbivores.

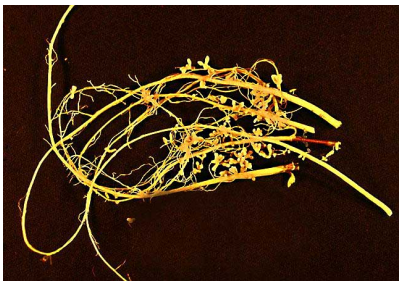

Figure: **Root nodules on a legume**: Soybean root nodules, each containing billions of Bradyrhizobium bacteria.

Endophytes may be transmitted either vertically (directly from parent to offspring) or horizontally (from individual to unrelated individual). Vertically transmitted fungal endophytes are asexual and transmit via fungal hyphae penetrating the host’s seeds (e.g., Neotyphodium). Since their reproductive fitness is intimately tied to that of their host plant, these fungi are often mutualistic. Conversely, horizontally transmitted fungal endophytes are sexual and transmit via spores that can be spread by wind and/or insect vectors. Since they spread in a similar way to pathogens, horizontally transmitted endophytes are often closely related to pathogenic fungi, although they are not pathogenic themselves.

Endophytes may benefit host plants by preventing pathogenic organisms from colonizing them. Extensive colonization of the plant tissue by endophytes creates a “barrier effect,” where the local endophytes outcompete and prevent pathogenic organisms from taking hold. Endophytes may also produce chemicals which inhibit the growth of competitors, including pathogenic organisms. Some bacterial endophytes have proven to increase plant growth. The presence of fungal endophytes can cause higher rates of water loss in leaves. However, certain fungal endophytes help plants survive drought and heat. Plant use of endophytic fungi in defense is a very common phenomenon, primarily involving the arbuscular mycorrhizal fungi.

The wide range of compounds produced by endophytes have been shown to combat pathogens and even cancers in animals including humans. One notable endophyte with medicinal benefits to humans was discovered by Gary Strobel: Pestalotiopsis microspora, an endophytic fungus of Taxus wallachiana (Himalayan Yew) was found to produce taxol. Endophytes are also being investigated for roles in agriculture and biofuels production. Inoculating crop plants with certain endophytes may provide increased disease or parasite resistance while others may possess metabolic processes that convert cellulose and other carbon sources into “myco-diesel” hydrocarbons and hydrocarbon derivatives. Piriformospora indica is an interesting endophytic fungus of the order Sebacinales, the fungus is capable of colonizing roots and forming symbiotic relationship with every possible plant on earth. P.

indica has also been shown to increase both crop yield and plant defence of a variety of crops (barley, tomato, maize, etc.) against root-pathogens.

It is speculated that there may be many thousands of endophytes useful to mankind. However, since there are few scientists working in this field, and since forests and areas of biodiversity are rapidly being destroyed, many useful endophytes for curing disease might be permanently lost for medicinal use before they are discovered. The effects of climate change on endophytes are being investigated. Studies of plants grown at different climates or at increased carbon dioxide levels have different distributions of endophytic species.

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16.2F: Mycorrhizae: The Symbiotic Relationship between Fungi and Roots

Many plants form associations called mycorrhizae with fungi that give them access to nutrients in the soil, protecting against disease and toxicities.

Learning Objectives

- Describe the symbiotic relationship of mycorrhizae and plant roots

Key Points

- Because nutrients are often depleted in the soil, most plants form symbiotic relationships called mycorrhizae with fungi that integrate into the plant's root.
- The relationship between plants and fungi is symbiotic because the plant obtains phosphate and other minerals through the fungus, while the fungus obtains sugars from the plant root.
- The long extensions of the fungus, called hyphae, help increase the surface area of the plant root system so that it can extend beyond the area of nutrient depletion.
- Ectomycorrhizae are a type of mycorrhizae that form a dense sheath around the plant roots, called a mantle, from which the hyphae grow; in endomycorrhizae, mycelium is embedded within the root tissue, as opposed to forming a sheath around it.
- In endomycorrhizae, mycelium is embedded within the root tissue, as opposed to forming a sheath around it; these are found in the roots of most terrestrial plants.

Key Terms

- **mycorrhiza**: a symbiotic association between a fungus and the roots of a vascular plant
- **hypha**: a long, branching, filamentous structure of a fungus that is the main mode of vegetative growth
- **mycelium**: the vegetative part of any fungus, consisting of a mass of branching, threadlike hyphae, often underground

Mycorrhizae: The Symbiotic Relationship between Fungi and Roots



Mycorrhizae: Hyphae proliferate within the mycorrhizae, which appears as off-white fuzz in this image. These hyphae greatly increase the surface area of the plant root, allowing it to reach areas that are not depleted of nutrients.

A nutrient depletion zone can develop when there is rapid soil solution uptake, low nutrient concentration, low diffusion rate, or low soil moisture. These conditions are very common; therefore, most plants rely on fungi to facilitate the uptake of minerals from the soil. Mycorrhizae, known as root fungi, form symbiotic associations with plant roots. In these associations, the fungi are actually integrated into the physical structure of the root. The fungi colonize the living root tissue during active plant growth.



Figure: **Ectomycorrhizae**: Ectomycorrhizae form sheaths, called a mantle, around the roots of plants, as shown in this image.

Through mycorrhization, the plant obtains phosphate and other minerals, such as zinc and copper, from the soil. The fungus obtains nutrients, such as sugars, from the plant root. Mycorrhizae help increase the surface area of the plant root system because hyphae, which are narrow, can spread beyond the nutrient depletion zone. Hyphae are long extensions of the fungus, which can grow into small soil pores that allow access to phosphorus otherwise unavailable to the plant. The beneficial effect on the plant is best observed in poor soils. The benefit to fungi is that they can obtain up to 20 percent of the total carbon accessed by plants. Mycorrhizae function as a physical barrier to pathogens. They also provides an induction of generalized host defense mechanisms, which sometimes involves the production of antibiotic compounds by the fungi. Fungi have also been found to have a protective role for plants rooted in soils with high metal concentrations, such as acidic and contaminated soils.

There are two types of mycorrhizae: ectomycorrhizae and endomycorrhizae. Ectomycorrhizae form an extensive dense sheath around the roots, called a mantle. Hyphae from the fungi extend from the mantle into the soil, which increases the surface area for water and mineral absorption. This type of mycorrhizae is found in forest trees, especially conifers, birches, and oaks. Endomycorrhizae, also called arbuscular mycorrhizae, do not form a dense sheath over the root. Instead, the fungal mycelium is embedded within the root tissue. Endomycorrhizae are found in the roots of more than 80 percent of terrestrial plants.

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16.2F: Plant Pathogens

There are four main bacterial pathogenicity factors: cell wall degrading enzymes, toxins, phytohormones, and effector proteins.

Learning Objectives

- Break down the types and modes of plant pathogenicity

Key Points

- The majority of phytopathogenic fungi belong to the Ascomycetes and the Basidiomycetes.
- Many soil inhabiting fungi are capable of living saprotrophically, carrying out the part of their lifecycle in the soil.
- Bacterial plant pathogens are much more prevalent in sub-tropical and tropical regions of the world.

Key Terms

- **Type three secretion system**: Type three secretion system (often written Type III secretion system and abbreviated TTSS or T3SS, also called Injectisome or Injectosome) is a protein appendage found in several Gram-negative bacteria. In pathogenic bacteria, the needle-like structure is used as a sensory probe to detect the presence of eukaryotic organisms and secrete proteins that help the bacteria infect them. The proteins are secreted directly from the bacterial cell into the eukaryotic cell, also known as “the host” cell.

Most bacteria that are associated with plants are actually saprophytic, and do no harm to the plant itself. However, a small number, around 100 species, are able to cause disease. Bacterial diseases are much more prevalent in sub-tropical and tropical regions of the world. Most plant pathogenic bacteria are rod shaped (bacilli). In order to be able to colonise the plant they have specific pathogenicity factors. There are 4 main bacterial pathogenicity factors:



Figure: **Tobacco Mosaic Disease**: Photo of a tobacco leaf with symptoms of tobacco mosaic virus.

- Cell wall -degrading enzymes: These are used to break down the plant cell wall in order to release the nutrients inside.
- Toxins: These can be non- host -specific, which damage all plants, or host-specific, which cause damage only on a host plant.
- Phytohormones: example Agrobacterium changes the level of Auxin to cause tumours.
- Effector proteins: These can be secreted into the extracellular environment or directly into the host cell, often via the Type three secretion system. Some effectors are known to suppress host defense processes. This can include: reducing the plants internal signaling mechanisms or reduction of phytochemicals production. Bacteria, fungus and oomycetes are known for this function.

Significant bacterial plant pathogens:

- Burkholderia
- Proteobacteria
- *Xanthomonas* spp.
- *Pseudomonas* spp.
- Pseudomonas syringae pv. tomato causes tomato plants to produce less fruit, and it “continues to adapt to the tomato by minimizing its recognition by the tomato immune system. “

The majority of phytopathogenic fungi belong to the Ascomycetes and the Basidiomycetes. The fungi reproduce both sexually and asexually via the production of spores and other structures. Spores may be spread long distances by air or water, or they may be soil borne. Many soil inhabiting fungi are capable of living saprotrophically, carrying out the part of their lifecycle in the soil. These are known as facultative saprotrophs. Fungal diseases may be controlled through the use of fungicides and other agriculture practices, however new races of fungi often evolve that are resistant to various fungicides. · Biotrophic fungal pathogens colonize living plant

tissue and obtain nutrients from living host cells. Necrotrophic fungal pathogens infect and kill host tissue and extract nutrients from the dead host cells.

Significant fungal plant pathogens include:

- *Fusarium* spp. (causal agents of Fusarium wilt disease)
- *Thielaviopsis* spp. (causal agents of: canker rot, black root rot, *Thielaviopsis* root rot)
- *Verticillium* spp.
- *Magnaporthe grisea* (causal agent of blast of rice and gray leaf spot in turfgrasse

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16.2G: Nitrogen Fixation: Root and Bacteria Interactions

Plants cannot extract the necessary nitrogen from soil, so they form symbiotic relationships with rhizobia that can fix it as ammonia.

Learning Objectives

- Explain the process and importance of nitrogen fixation

Key Points

- Diatomic nitrogen is abundant in the atmosphere and soil, but plants are unable to use it because they do not have the necessary enzyme, nitrogenase, to convert it into a form that they can use to make proteins.
- Soil bacteria, or rhizobia, are able to perform biological nitrogen fixation in which atmospheric nitrogen gas (N_2) is converted into the ammonia (NH_3) that plants are able to use to synthesize proteins.
- Both the plants and the bacteria benefit from the process of nitrogen fixation; the plant obtains the nitrogen it needs to synthesize proteins, while the bacteria obtain carbon from the plant and a secure environment to inhabit within the plant roots.

Key Terms

- **rhizobia**: any of various bacteria, of the genus Rhizobium, that form nodules on the roots of legumes and fix nitrogen
- **nitrogen fixation**: the conversion of atmospheric nitrogen into ammonia and organic derivatives, by natural means, especially by microorganisms in the soil, into a form that can be assimilated by plants
- **nodule**: structures that occur on the roots of plants that associate with symbiotic nitrogen-fixing bacteria

Nitrogen Fixation: Root and Bacteria Interactions

Nitrogen is an important macronutrient because it is part of nucleic acids and proteins. Atmospheric nitrogen, which is the diatomic molecule N_2, or dinitrogen, is the largest pool of nitrogen in terrestrial ecosystems. However, plants cannot take advantage of this nitrogen because they do not have the necessary enzymes to convert it into biologically useful forms. However, nitrogen can be "fixed." It can be converted to ammonia (NH_3) through biological, physical, or chemical processes. Biological nitrogen fixation (BNF), the conversion of atmospheric nitrogen (N_2) into ammonia (NH_3), is exclusively carried out by prokaryotes, such as soil bacteria or cyanobacteria. Biological processes contribute 65 percent of the nitrogen used in agriculture.

The most important source of BNF is the symbiotic interaction between soil bacteria and legume plants, including many crops important to humans. The NH_3 resulting from fixation can be transported into plant tissue and incorporated into amino acids, which are then made into plant proteins. Some legume seeds, such as soybeans and peanuts, contain high levels of protein and are among the most important agricultural sources of protein in the world.

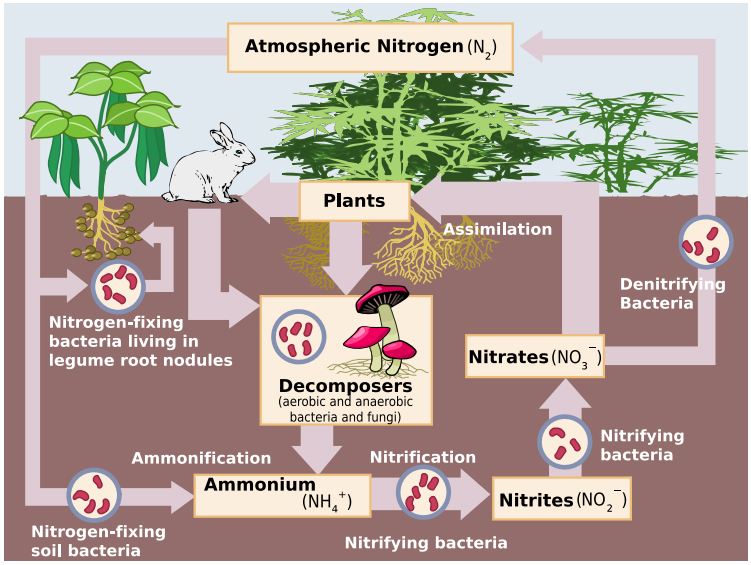

Figure: **Diagram of the Nitrogen Cycle**: Schematic representation of the nitrogen cycle. Abiotic nitrogen fixation has been omitted.



Figure: **Nitrogen fixation in crops**: Some common edible legumes, such as (a) peanuts, (b) beans, and (c) chickpeas, are able to interact symbiotically with soil bacteria that fix nitrogen.

Soil bacteria, collectively called rhizobia, symbiotically interact with legume roots to form specialized structures called nodules in which nitrogen fixation takes place. This process entails the reduction of atmospheric nitrogen to ammonia by means of the enzyme nitrogenase. Therefore, using rhizobia is a natural and environmentally-friendly way to fertilize plants as opposed to chemical fertilization that uses a non-renewable resource, such as natural gas. Through symbiotic nitrogen fixation, the plant benefits from using an endless source of nitrogen from the atmosphere. The process simultaneously contributes to soil fertility because the plant root system leaves behind some of the biologically-available nitrogen. As in any symbiosis, both organisms benefit from the interaction: the plant obtains ammonia and bacteria obtain carbon compounds generated through photosynthesis, as well as a protected niche in which to grow.

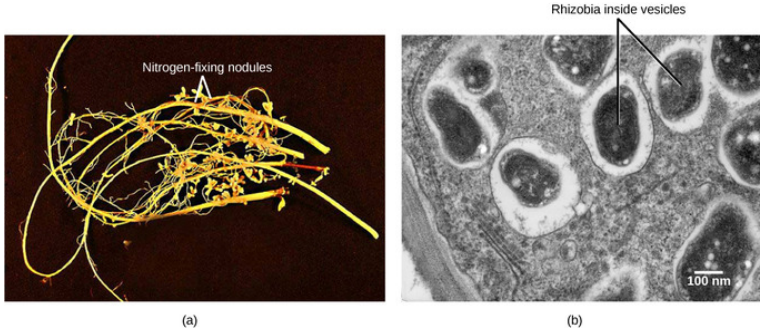

Figure: **Rhizobia**: Soybean roots contain (a) nitrogen-fixing nodules. Cells within the nodules are infected with Bradyrhyzobium japonicum, a rhizobia or “root-loving” bacterium. The bacteria are encased in (b) vesicles inside the cell, as can be seen in this transmission electron micrograph.

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SECTION OVERVIEW

16.3: Aquatic Microbiology

Topic hierarchy

16.3A: Marine Habitats

16.3B: Planktonic Communities

16.3C: Planktonic Food Webs

16.3D: Ocean Floor

16.3E: Cold-Seep Ecosystems

16.3F: The Deep Sea and Barophilism

16.3G: Sea Coral and Sea Anemone Zooxanthellae

16.3H: Sponge Communities

16.3I: Freshwater Environments

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16.3A: Marine Habitats

The marine environment supplies many kinds of habitats that support marine life.

Learning Objectives

- Describe marine habitats

Key Points

- Marine habitats can be divided into coastal and open ocean habitats.
- Coastal habitats are found in the area that extends from as far as the tide comes in on the shoreline out to the edge of the continental shelf.
- Open ocean habitats are found in the deep ocean beyond the edge of the continental shelf.
- Most marine life is found in coastal habitats, even though the shelf area occupies only seven percent of the total ocean area.

Key Terms

- **coastal**: Relating to the coast; on or near the coast, as a coastal town, a coastal breeze.
- **habitat**: A specific place or natural conditions in which a plant or animal lives.
- **marine**: Of, or pertaining to, the sea (marine biology, marine insurance).

The marine environment supplies many kinds of habitats that support life. Marine life partially depends on the saltwater that is in the sea ("marine" comes from the Latin "mare," meaning sea or ocean). A habitat is an ecological or environmental area inhabited by one or more living species.



Figure: **Marine Habitats**: Coral reefs provide marine habitats for tube sponges, which in turn become marine habitats for fishes.

Marine habitats can be divided into coastal and open ocean habitats. Coastal habitats are found in the area that extends from as far as the tide comes in on the shoreline, out to the edge of the continental shelf. Most marine life is found in coastal habitats, even though the shelf area occupies only seven percent of the total ocean area. Open ocean habitats are found in the deep ocean beyond the edge of the continental shelf.

Alternatively, marine habitats can be divided into pelagic and demersal habitats. Pelagic habitats are found near the surface or in the open water column, away from the bottom of the ocean. Demersal habitats are near or on the bottom of the ocean. An organism living in a pelagic habitat is said to be a pelagic organism, as in pelagic fish. Similarly, an organism living in a demersal habitat is said to be a demersal organism, as in demersal fish. Pelagic habitats are intrinsically shifting and ephemeral, depending on what ocean currents are doing.

Marine habitats can be modified by their inhabitants. Some marine organisms, like corals, kelp, mangroves and seagrasses, are ecosystem engineers, which reshape the marine environment to the point where they create habitats for other organisms.

Marine habitats include coastal zones, intertidal zones, sandy shores, rocky shores, mudflats, swamps and salt marshes, estuaries, kelp forests, seagrasses, and coral reefs. In addition, in the open ocean there are surface waters, deep sea and sea floor.

Intertidal zones (those areas close to shore) are constantly being exposed and covered by the ocean's tides. A huge array of life lives within this zone.

Sandy shores, also called beaches, are coastal shorelines where sand accumulates. Waves and currents shift the sand, continually building and eroding the shoreline. Longshore currents flow parallel to the beaches, making waves break obliquely on the sand. These currents transport large amounts of sand along coasts, forming spits, barrier islands and tombolos. Longshore currents also commonly create offshore bars, which give beaches some stability by reducing erosion.

The relative solidity of rocky shores seems to give them a permanence compared to the shifting nature of sandy shores. This apparent stability is not real over even quite short geological time scales, but it is real enough over the short life of an organism. In contrast to sandy shores, plants and animals can anchor themselves to the rocks.

Mudflats are coastal wetlands that form when mud is deposited by tides or rivers. They are found in sheltered areas such as bays, bayous, lagoons, and estuaries. Mudflats may be viewed geologically as exposed layers of bay mud, resulting from deposition of estuarine silts, clays and marine animal detritus. Most of the sediment within a mudflat is within the intertidal zone, and thus the flat is submerged and exposed approximately twice daily.

Mangrove swamps and salt marshes form important coastal habitats in topical and temperate areas respectively. An estuary is a partly enclosed coastal body of water with one or more rivers or streams flowing into it, and with a free connection to the open sea.

Kelp forests are underwater areas with a high density of kelp. They are recognized as one of the most productive and dynamic ecosystems on Earth. Smaller areas of anchored kelp are called kelp beds. Kelp forests occur worldwide throughout temperate and polar coastal oceans.

Seagrasses are flowering plants from one of four plant families which grow in marine environments. They are called seagrasses because the leaves are long and narrow and are very often green, and because the plants often grow in large meadows, which look like grassland.

Reefs comprise some of the densest and most diverse habitats in the world. The best-known types of reefs are tropical coral reefs, which exist in most tropical waters; however, reefs can also exist in cold water. Reefs are built up by corals and other calcium-depositing animals, usually on top of a rocky outcrop on the ocean floor. Reefs can also grow on other surfaces; this has made it possible to create artificial reefs. Coral reefs also support a huge community of life, including the corals themselves, their symbiotic zooxanthellae, tropical fish, and many other organisms.

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16.3B: Planktonic Communities

Plankton (singular plankter) are any organisms that live in the water column and are incapable of swimming against a current.

Learning Objectives

- Recall Planktonic communities

Key Points

- Plankton are primarily divided into broad functional (or trophic level) groups: Phytoplankton, Zooplankton, and Bacterioplankton.
- Plankton cover a wide range of sizes, including microscopic to large organisms such as jellyfish.
- Plankton community into broad producer, consumer, and recycler groups.

Key Terms

- **trophic**: Describing the relationships between the feeding habits of organisms in a food chain.
- **plankton**: Plankton (singular plankter) are any organisms that live in the water column and are incapable of swimming against a current. They provide a crucial source of food to many large aquatic organisms, such as fish and whales.
- **organisms**: An organism is any contiguous living system (such as animal, fungus, micro-organism, or plant). In at least some form, all types of organisms are capable of response to stimuli, reproduction, growth and development, and maintenance of homeostasis as a stable whole.

Plankton (singular plankter) are any organisms that live in the water column and are incapable of swimming against a current. They provide a crucial source of food to many large aquatic organisms, such as fish and whales.

These organisms include drifting animals, plants, archaea, algae, or bacteria that inhabit the pelagic zone of oceans, seas, or bodies of fresh water. That is, plankton are defined by their ecological niche rather than phylogenetic or taxonomic classification.

Although many planktic (or planktonic) species are microscopic in size, plankton consists organisms covering a wide range of sizes, including large organisms such as jellyfish.

Plankton are primarily divided into broad functional (or trophic level) groups: Phytoplankton, Zooplankton, and Bacterioplankton.

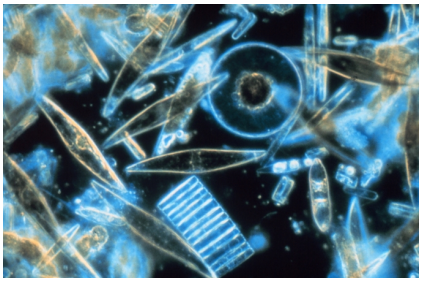

Figure: **Diatoms**: Assorted diatoms as seen through a microscope. These specimens were living between crystals of annual sea ice in McMurdo Sound, Antarctica. Image digitized from original 35mm Ektachrome slide. These tiny phytoplankton are encased within a silicate cell wall.

Phytoplankton (from Greek phyton, or plant), autotrophic, prokaryotic, or eukaryotic algae live near the water surface where there is sufficient light to support photosynthesis. Among the more important groups are the diatoms, cyanobacteria, dinoflagellates, and coccolithophores.

Zooplankton (from Greek zoon, or animal), small protozoans or metazoans (e.g. crustaceans and other animals) that feed on other plankton and telonemia. Some of the eggs and larvae of larger animals, such as fish, crustaceans, and annelids, are included here.

Bacterioplankton, bacteria and archaea, which play an important role in remineralising organic material down the water column (note that the prokaryotic phytoplankton are also bacterioplankton).

This scheme divides the plankton community into broad producer, consumer, and recycler groups. However, determining the trophic level of some plankton is not straightforward. For example, although most dinoflagellates are either photosynthetic producers or heterotrophic consumers, many species are mixotrophic depending upon circumstances.

Aside from representing the bottom few levels of a food chain that supports commercially important fisheries, plankton ecosystems play a role in the biogeochemical cycles of many important chemical elements, including the ocean's carbon cycle.

Primarily by grazing on phytoplankton, zooplankton provides carbon to the planktic foodweb, either respiring it to provide metabolic energy, or upon death as biomass or detritus. Typically more dense than seawater, organic material tends to sink. In open ocean ecosystems away from the coasts this transports carbon from surface waters to the deep. This process is known as the biological pump, and is one reason that oceans constitute the largest carbon sink on earth.

It might be possible to increase the ocean's uptake of carbon dioxide generated through human activities by increasing plankton production through "seeding," primarily with the micronutrient iron. However, this technique may not be practical at a large scale. Ocean oxygen depletion and resultant methane production (caused by the excess production remineralizing at depth) is one potential drawback.

The growth of phytoplankton populations is dependent on light levels and nutrient availability. The main factor limiting growth varies from region to region in the world's oceans. On a broad scale, growth of phytoplankton in the oligotrophic tropical and subtropical gyres is generally limited by nutrient supply, while light often limits phytoplankton growth in subarctic gyres. Environmental variability at multiple scales influences the nutrient and light available for phytoplankton. As these organisms form the base of the marine food web, this variability in phytoplankton growth influences higher trophic levels. For example, at interannual scales phytoplankton levels temporarily plummet during El Nino periods, influencing populations of zooplankton, fishes, sea birds, and marine mammals.

The effects of anthropogenic warming on the global population of phytoplankton are an area of active research. Changes in the vertical stratification of the water column, the rate of temperature-dependent biological reactions, and the atmospheric supply of nutrients are expected to have important impacts on future phytoplankton productivity. Additionally, changes in the mortality of phytoplankton due to rates of zooplankton grazing may be significant.

Freshly hatched fish larvae are also plankton for a few days as long as they cannot swim against currents. Zooplankton are the initial prey item for almost all fish larvae as they switch from their yolk sacs to external feeding. Fish rely on the density and distribution of zooplankton to match that of new larvae, which can otherwise starve. Natural factors (e.g., current variations) and man-made factors (e.g. river dams) can strongly affect zooplankton, which can in turn strongly affect larval survival and therefore breeding success.

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16.3C: Planktonic Food Webs

Plankton communities are divided into broad categories of producer, consumer, and recycler groups.

Learning Objectives

- Differentiate planktonic food webs

Key Points

- Plankton communities represent the bottom few levels of a food chain that supports commercially important fisheries.
- Plankton ecosystems also play a crucial role in the biogeochemical cycles of many important chemical elements, including the ocean's carbon cycle.
- The growth of phytoplankton populations is dependent on light levels and nutrient availability.

Key Terms

- **plankton**: Plankton (singular plankter) are any organisms that live in the water column and are incapable of swimming against a current. They provide a crucial source of food to many large aquatic organisms, such as fish and whales.
- **ecosystems**: Communities of living organisms (plants, animals and microbes) in conjunction with the nonliving components of their environment (things like air, water, and mineral soil), interacting as a system; linked together through nutrient cycles and energy flows.
- **biogeochemical cycles**: A biogeochemical cycle or substance turnover or cycling of substances is a pathway by which a chemical element or molecule moves through both biotic (biosphere) and abiotic (lithosphere, atmosphere, and hydrosphere) compartments of Earth. A cycle is a series of change which comes back to the starting point and which can be repeated.

Plankton communities are divided into broad categories of producer, consumer and recycler groups. However, determining the trophic level of some plankton is not straightforward. For example, although most dinoflagellates are either photosynthetic producers or heterotrophic consumers, many species are mixotrophic, depending upon circumstances.



Figure: **Photomontage of plankton organisms**: Plankton are any water-column organisms that are incapable of swimming against a current.

Aside from representing the bottom few levels of a food chain that supports commercially important fisheries, plankton ecosystems play a role in the biogeochemical cycles of many important chemical elements, including the ocean's carbon cycle.

Primarily by grazing on phytoplankton, zooplankton provide carbon to the planktic foodweb, either respiring it to provide metabolic energy, or upon death as biomass or detritus. Typically more dense than seawater, organic material tends to sink. In open-ocean ecosystems away from the coasts this transports carbon from surface waters to the deep. This process is known as the biological pump, and is one reason that oceans constitute the largest carbon sink on Earth.

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16.3D: Ocean Floor

Ocean floor extremophile chemosynthetic microbes provide energy and carbon to the other organisms in these environments.

Learning Objectives

- Explain the importance of microbes and hydrothermal vents to underwater ecosystems

Key Points

- Recently, there has been the discovery of abundant marine life in the deep sea, especially around hydrothermal vents.
- Hydrothermal vents along the mid-ocean ridge spreading centers act as oases and support unique biomes and many new microbes.
- Each area of the seabed has typical features such as common soil composition, typical topography, salinity of water layers above it, marine life, magnetic direction of rocks, and sedimenting.

Key Terms

- **plankton**: Plankton (singular plankter) are any organisms that live in the water column and are incapable of swimming against a current. They provide a crucial source of food to many large aquatic organisms, such as fish and whales.
- **ecosystems**: Communities of living organisms (plants, animals and microbes) in conjunction with the nonliving components of their environment (things like air, water, and mineral soil), interacting as a system; linked together through nutrient cycles and energy flows.
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Microorganisms, by their omnipresence, impact the entire biosphere. Microbial life plays a primary role in regulating biogeochemical systems in virtually all of our planet ‘s environments, including some of the most extreme, from frozen environments and acidic lakes, to hydrothermal vents at the bottom of deepest oceans, and some of the most familiar, such as the human small intestine.

Microbes, especially bacteria, often engage in symbiotic relationships (either positive or negative) with other organisms, and these relationships affect the ecosystem. One example of these fundamental symbioses are chloroplasts, which allow eukaryotes to conduct photosynthesis. Chloroplasts are considered to be endosymbiotic cyanobacteria, a group of bacteria that are thought to be the origins of aerobic photosynthesis.

They are the backbone of all ecosystems, but even more so in the zones where light cannot approach and therefore photosynthesis cannot be the basic means to collect energy. In such zones, chemosynthetic microbes provide energy and carbon to the other organisms. Other microbes are decomposers, with the ability to recycle nutrients from other organisms’ waste poducts. These microbes play a vital role in biogeochemical cycles. The nitrogen cycle, the phosphorus cycle and the carbon cycle all depend on microorganisms in one way or another. For example, nitrogen which makes up 78% of the planet’s atmosphere is “indigestible” for most organisms, and the flow of nitrogen into the biosphere depends on a microbial process called fixation.

Recently there has been the discovery of abundant marine life in the deep sea, especially around hydrothermal vents. Large deep sea communities of marine life have been discovered around black and white smokers – hydrothermal vents emitting typical chemicals toxic to humans and most of the vertebrates. This marine life receives its energy from both the extreme temperature difference (typically a drop of 150 degrees) and from chemosynthesis by bacteria.

Brine pools are another seabed feature, usually connected to cold seeps. Hydrothermal vents along the mid-ocean ridge spreading centers act as oases, as do their opposites, cold seeps. Such places support unique biomes and many new microbes and other lifeforms have been discovered at these locations. The deepest recorded oceanic trench measured to date is the Mariana Trench, near the Philippines, in the Pacific Ocean at 10,924 m (35,838 ft). At such depths, water pressure is extreme. There is no sunlight, but some life still exists. A white flatfish, a shrimp, and a jellyfish were seen by the American crew of the bathyscaphe Trieste when it dove to the bottom in 1960. Marine life also flourishes around seamounts that rise from the depths, where fish and other sea life congregate to spawn and feed.

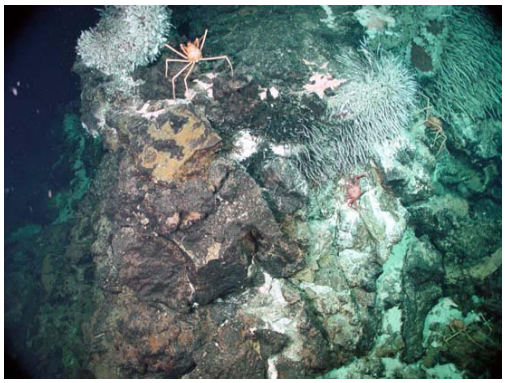

Figure: Zooarium chimney provides a habitat for vent biota.

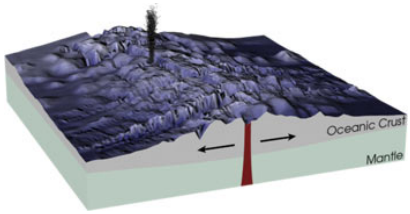

Figure: **Oceanic ridge with deep sea vent**: Oceanic ridge with deep sea vent.

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16.3E: Cold-Seep Ecosystems

A cold seep is an area of the ocean floor where hydrogen sulfide, methane, and other hydrocarbon-rich fluid seepage occurs.

Learning Objectives

- Outline the organisms that live in cold-seep ecosystems

Key Points

- Cold seeps develop unique topography over time, where reactions between methane and seawater create carbonate rock formations and reefs.
- Types of cold seeps can be distinguished according to the depth, as shallow cold seeps and deep cold seeps.
- Organisms living in cold seeps are known as extremophiles.

Key Terms

- **cold seep**: A cold seep (sometimes called a cold vent) is an area of the ocean floor where hydrogen sulfide, methane, and other hydrocarbon-rich fluid seepage occurs, often in the form of a brine pool. “Cold” does not mean temperature of seepage is lower than surrounding sea water. Actually, its temperature is often slightly higher.
- **topography**: A detailed graphic representation of the surface features of a place or object.
- **extremophiles**: An extremophile (from Latin extremus, meaning “extreme,” and Greek philiā (φ), meaning “love”) is an organism that thrives in physically or geochemically extreme conditions that are detrimental to most life on earth.

A cold seep (sometimes called a cold vent) is an area of the ocean floor where hydrogen sulfide, methane, and other hydrocarbon-rich fluid seepage occurs, often in the form of a brine pool. “Cold” does not mean temperature of seepage is lower than surrounding sea water. Actually, its temperature is often slightly higher. Cold seeps constitute a biome supporting several endemic species.

Cold seeps develop unique topography over time, where reactions between methane and seawater create carbonate rock formations and reefs. These reactions may also be dependent on bacterial activity. Ikaite, a hydrous calcium carbonate, can be associated with oxidizing methane at cold seeps.

Types of cold seeps can be distinguished according to the depth, as shallow cold seeps and deep cold seeps. Cold seeps can also be distinguished in detail, as follows: oil/gas seeps, gas seeps, methane seeps, gas hydrate seeps, brine seeps, are forming brine pools, pockmarks and mud volcanos.

Organisms living in cold seeps are known as extremophiles. Biological research in cold seeps and hydrothermal vents has been mostly focused on the microbiology and the prominent chemosynthetic macro-invertebrates. Much less research has been done on the smaller benthic fraction at the size of the meiofauna (<1 mm).

Community composition’s orderly shift from one set of species to another is called ecological succession. The first type of organism to take advantage of this deep-sea energy source is bacteria. Aggregating into bacterial mats at cold seeps, these bacteria metabolize methane and hydrogen sulfide (another gas that emerges from seeps) for energy. This process of obtaining energy from chemicals is known as chemosynthesis.

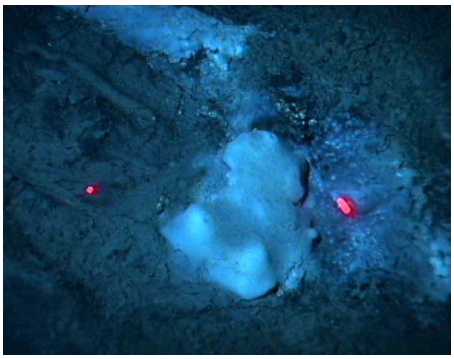

Figure: **A Beggiatoa bacterial mat at the Blake Ridge**: Beggiatoa spp. bacterial mat at a seep on Blake Ridge, off the coast of South Carolina. The red dots are range-finding laser beams. Beggiatoa are able to detoxify hydrogen sulfide in soil.

During this initial stage, when methane is relatively abundant, dense mussel beds also form near the cold seep. Mostly composed of species in the genus Bathymodiolus, these mussels do not directly consume food. Instead, they are nourished by symbiotic bacteria that also produce energy from methane, similar to their relatives that form mats. Chemosynthetic bivalves are prominent constituents of the fauna of cold seeps and are represented in that setting by five families: Solemyidae, Lucinidae, Vesicomyidae, Thyasiridae, and Mytilidae.

This microbial activity produces calcium carbonate (CaCO3), which is deposited on the seafloor and forms a layer of rock. During a period lasting up to several decades, these rock formations attract siboglinid tubeworms, which settle and grow along with the mussels. Like the mussels, tubeworms rely on chemosynthetic bacteria (in this case, a type that needs hydrogen sulfide instead of methane) for survival. True to any symbiotic relationship, a tubeworm also provides for their bacteria by appropriating hydrogen sulfide from the environment. The sulfide not only comes from the water, but is also mined from the sediment through an extensive "root" system a tubeworm "bush" establishes in the hard, carbonate substrate. A tubeworm bush can contain hundreds of individual worms, which can grow a meter or more above the sediment.

Cold seeps do not last indefinitely. As the rate of gas seepage slowly decrease, the shorter-lived, methane-hungry mussels (or more precisely, their methane-hungry bacterial symbionts) start to die off. At this stage, tubeworms become the dominant organism in a seep community. As long as there is some sulfide in the sediment, the sulfide-mining tubeworms can persist. Individuals of one tubeworm species Lamellibrachia luymesi have been estimated to live for over 250 years in such conditions.

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16.3F: The Deep Sea and Barophilism

A piezophile (also called a barophile) is an organism which thrives at high pressures, such as deep sea bacteria or archaea.

Learning Objectives

- Indicate how barophiles survive in the deep sea

Key Points

- The three main sources of energy and nutrients for deep sea communities are marine snow, whale falls, and chemosynthesis.
- Zones of the deep sea include the mesopelagic zone, the bathyal zone, the abyssal zone, and the hadal zone.
- Organisms have adapted in novel ways to become tolerant of the high pressures and cool temperatures in order to colonize deep sea habitats.

Key Terms

- **deep sea**: The deeper part of the sea or ocean in which no light penetrates.
- **piezophile**: A piezophile (also called a barophile) is an organism which thrives at high pressures, such as deep sea bacteria or archaea.
- **chemosynthesis**: The production of carbohydrates and other compounds from simple compounds such as carbon dioxide, using the oxidation of chemical nutrients as a source of energy rather than sunlight; it is limited to certain bacteria and fungi.

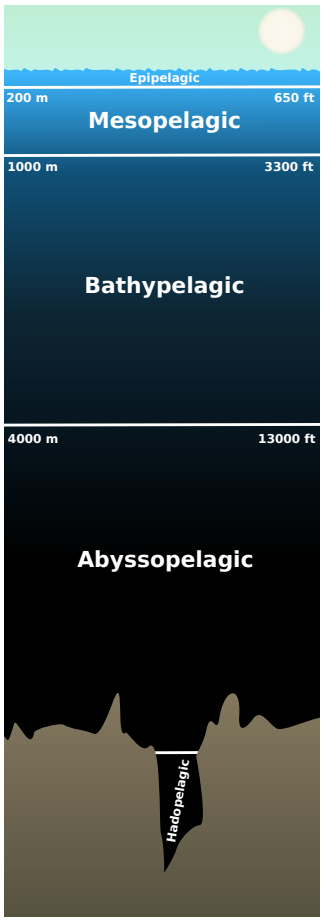

Figure: **Deep Sea Pelagic Zones**: Mesopelagic, bathyl, abyssal, and hadal zones.

Deep sea communities currently remain largely unexplored, due the technological and logistical challenges, and the expense involved in visiting these remote biomes. Because of the unique challenges (particularly the high barometric pressure, extremes of temperature, and absence of light), it was long believed that little life existed in this hostile environment. Since the 19th century however, research has demonstrated that significant biodiversity exists in the deep sea.

The three main sources of energy and nutrients for deep sea communities are marine snow, whale falls, and chemosynthesis at hydrothermal vents and cold seeps.

Zones of the deep sea include the mesopelagic zone, the bathyal zone, the abyssal zone, and the hadal zone.

A piezophile, also called a barophile, is an organism which thrives at high pressures, such as deep sea bacteria or archaea. They are generally found on ocean floors, where pressure often exceeds 380 atm (38 MPa). Some have been found at the bottom of the Pacific Ocean where the maximum pressure is roughly 117 MPa. The high pressures experienced by these organisms can cause the normally fluid cell membrane to become waxy and relatively impermeable to nutrients. These organisms have adapted in novel ways to become tolerant of these pressures in order to colonize deep sea habitats. One example, xenophyophores, have been found in the deepest ocean trench, 6.6 miles (10,541 meters) below the surface.

Barotolerant bacteria are able to survive at high pressures, but can exist in less extreme environments as well. Obligate barophiles cannot survive outside of such environments. For example, the Halomonas species Halomonas salaria requires a pressure of 1000 atm (100 MPa) and a temperature of three degrees Celsius. Most piezophiles grow in darkness and are usually very UV-sensitive; they lack many mechanisms of DNA repair.

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16.3G: Sea Coral and Sea Anemone Zooxanthellae

Zooxanthellae refers to a variety of species that form symbiotic relationships with other marine organisms, particularly coral.

Learning Objectives

- Outline the role Zooxanthellae play in animal sybiosis

Key Points

- Zooxanthellae species are members of the phylum Dinoflagellata. The most common genus is Symbiodinium.
- Each Symbiodinium cell is coccoid in hospite (living in a host cell) and surrounded by a membrane that originates from the host cell plasmalemma during phagocytosis.
- Zooxanthellates mutualistic relationships with reef-building corals form the basis of a highly diverse and productive ecosystem.

Key Terms

- **endosymbiont**: An organism that lives within the body or cells of another organism.
- **phagocytosis**: the process by which a cell incorporates foreign particles intracellularly.
- **benthic**: Pertaining to the benthos; living on the seafloor, as opposed to floating in the ocean.

Symbiodinium are colloquially called “zooxanthellae” (or “zoox”), and animals symbiotic with algae in this genus are said to be “zooxanthellate”. The term was loosely used to refer to any golden-brown endosymbionts, including diatoms and other dinoflagellates. The genus Symbiodinium encompasses the largest and most prevalent group of endosymbiotic dinoflagellates known to science. These unicellular algae commonly reside in the endoderm of tropical cnidarians such as corals, sea anemones, and jellyfish, where they translocate products of photosynthesis to the host and in turn receive inorganic nutrients (e.g. CO2, NH4+). They are also harbored by various species of sponges, flatworms, mollusks (e.g. giant clams), foraminifera (soritids), and some ciliates. Generally, these dinoflagellates enter the host cell through phagocytosis, persist as intracellular symbionts, reproduce, and disperse to the environment (note that in most mollusks, Symbiodinium are inter- rather than intra-cellular). Cnidarians that are associated with Symbiodinium occur mostly in warm oligotrophic (nutrient-poor) marine environments where they are often the dominant constituents of benthic communities. These dinoflagellates are therefore among the most abundant eukaryotic microbes found in coral reef ecosystems.

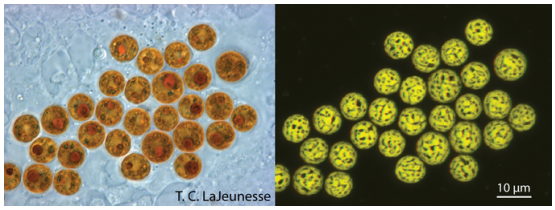

Figure: **Symbiodinium cell**: Symbiodinium cell living inside a jellyfish.

Symbiodinium are known primarily for their role as mutualistic endosymbionts. In hosts, they usually occur in high densities, ranging from hundreds of thousands to millions per square centimeter. The successful culturing of swimming gymnodinioid cells from coral led to the discovery that “zooxanthellae” were actually dinoflagellates. Each Symbiodinium cell is coccoid in hospite (living in a host cell) and surrounded by a membrane that originates from the host cell plasmalemma during phagocytosis. This membrane probably undergoes some modification to its protein content, which functions to limit or prevent phago-lysosome fusion. The vacuole structure containing the symbiont is therefore termed the symbiosome, and only a single symbiont cell is found within each symbiosome. It is unclear how this membrane expands to accommodate a dividing symbiont cell. Under normal conditions, symbiont and host cells exchange organic and inorganic molecules that enable the growth and proliferation of both partners.

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16.3H: Sponge Communities

Sponge reefs serve an important ecological function as habitat, breeding and nursery areas for fish and invertebrates.

Learning Objectives

- Compare the types of sponge communities

Key Points

- Sponge reefs are considered to be “living fossils”.
- Hexactinellids, or “glassy” sponges are characterized by a rigid framework of spicules made of silica.
- A unique feature of glassy sponges is that their tissues are made up almost entirely of syncytia.

Key Terms

- **silica**: Any of the silica group of the silicate minerals.
- **Sponge reefs**: Sponge reefs serve an important ecological function as habitat, breeding, and nursery areas for fish and invertebrates. The reefs are currently threatened by the fishery, offshore oil, and gas industries.
- **syncytia**: A syncytia (plural syncytia) is a multinucleate cell which can result from multiple cell fusions of uninuclear cells (i.e., cells with a single nucleus), in contrast to a coenocyte, which can result from multiple nuclear divisions without accompanying cytokinesis.

Sponge reefs serve an important ecological function as habitat, breeding, and nursery areas for fish and invertebrates. The reefs are currently threatened by the fishery, offshore oil, and gas industries. Attempts are being made to protect these unique ecosystems through fishery closures, and potentially the establishment of Marine Protected Areas (MAPs) around the sponge reefs.

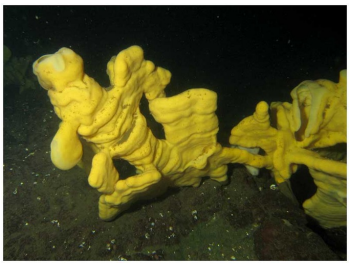

Figure: **Aphrocallistes vastus**: Aphrocallistes vastus (Cloud sponge), is a major reef-building species.

Hexactinellids

Hexactinellid sponge reefs were common in the late Jurassic period, and were believed to have gone extinct during or shortly after the Cretaceous period. Living sponge reefs were discovered in the Queen Charlotte Basin (QCB) in 1987-1988, and were reported in the Georgia Basin (GB) in 2005. These sponge reefs are considered to be “living fossils. ”

Hexactinellids, or “glassy” sponges, are characterized by a rigid framework of spicules made of silica. Unlike other poriferans, hexactinellids do not possess the ability to contract. Another unique feature of glassy sponges is that their tissues are made up almost entirely of syncytia. In a syncytium there are many nuclei in a continuous cytoplasm; nuclei are not packaged in discrete cells.

As a result, the sponge has a distinctive electrical conduction system across its body. This allows the sponge to rapidly respond to disturbances, such as a physical impact or excessive sediment in the water. The sponge’s response is to stop feeding. It will try to resume feeding after 20-30 minutes, but will stop again if the irritation is still present.

Hexactinellids are exclusively marine and are found throughout the world in deep (>1000 m) oceans. Individual sponges grow at a rate of 0-7 cm/year, and can live to be at least 220 years old. Little is known about hexactinellid sponge reproduction. Like all poriferans, the hexactinellids are filter feeders. They obtain nutrition from direct absorption of dissolved substances, and to a lesser extent from particulate materials. There are no known predators of healthy reef sponges. This is likely because the sponges possess very little organic tissue; the siliceous skeleton accounts for 90% of the sponge body weight.

Hexasterophorans

Hexasterophoran sponges have spicules called hexactines that have six rays set at right angles. Orders within hexasterophora are classified by how tightly the spicules interlock with Lyssanctinosan spicules less tightly interlocked than those of Hexactinosan sponges.

The primary frame-building sponges are all members of the order Hexactinosa, and include the species Chonelasma/Heterochone calyx (chalice sponge), Aphrocallistes vastus (cloud sponge), and Farrea occa. Hexactinosan sponges have a rigid scaffolding of "fused" spicules that persists after the death of the sponge.

Lyssactinosa

Other sponge species abundant on sponge reefs are members of the order Lyssactinosa (Rosselid sponges) and include Rhabdocalyptus dawsoni (boot sponge), Acanthascus platei, Acanthascus cactus and Staurocalyptus dowlingi. Rosselid sponges have a "woven" or "loose" siliceous skeleton that does not persist after the death of the sponge, and are capable of forming mats, but not reefs.

Sponge Reefs

Each living sponge on the surface of the reef can be over 1.5 m tall. The reefs are composed of mounds called "bioherms" that are up to 21 m high, and sheets called "biostromes" that are 2-10 m thick, and may be many km wide. Each sponge in the order Hexactinosa has a rigid skeleton that persists after the death of the animal. This provides an excellent substrate for sponge larvae to settle upon, and new sponges grow on the framework of past generations. The growth of sponge reefs is thus analogous to that of coral reefs. The tendrils of new sponges wrap around spicules of older, deceased sponges. The tendrils will later form the basal plate of the adult sponge that firmly anchors the animal to the reef.

Deep ocean currents carry fine sediments that are captured by the scaffolding of sponge reefs. A sediment matrix of silt, clay, and some sand forms around the base of the sponge bioherms. The sediment matrix is soft near the surface, and firm below one metre deep. Dead sponges become covered in sediment, but do not lose their supportive siliceous skeleton. The sponge sediments have high levels of silica and organic carbon. The reefs grow parallel to the glacial troughs, and the morphology of reefs is due to deep currents.

Hexactinellids first appeared in the fossil record during the late Proterozoic, and the first Hexactinosans were found in the late Devonian. Hexactinellid sponge reefs were first identified in the middle Triassic (245-208 million years ago). The sponges reached their full extent in the late Jurassic (208-146 million years ago), when a discontinuous reef system 7,000 km long stretched across the northern Tethys and North Atlantic basins. This chain of sponge reefs is the largest known biostructure to have ever existed on Earth.

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16.3I: Freshwater Environments

Fresh water is naturally occurring water on Earth which has low concentrations of dissolved salts and other total dissolved solids.

Learning Objectives

- Generalize the characteristics of freshwater environments

Key Points

- Freshwater habitats are divided into lentic systems (which are the stillwaters including ponds, lakes, swamps and mires) and lotic systems, which are running water; and groundwater which flows in rocks and aquifers.
- Fresh water creates a hypotonic environment for aquatic organisms.
- Most aquatic organisms have a limited ability to regulate their osmotic balance and therefore can only live within a narrow range of salinity.

Key Terms

- **hypotonic**: Having a lower osmotic pressure than another.
- **Freshwater**: Fresh water is naturally occurring water on the Earth's surface in ice sheets, ice caps, glaciers, bogs, ponds, lakes, rivers and streams, and underground as groundwater in aquifers and underground streams. Fresh water is generally characterized by having low concentrations of dissolved salts and other total dissolved solids.
- **osmotic balance**: Osmoregulation is the active regulation of the osmotic pressure of an organism's fluids to maintain the homeostasis of the organism's water content; that is, it keeps the organism's fluids from becoming too diluted or too concentrated.

Fresh water is naturally occurring water on the Earth's surface in ice sheets, ice caps, glaciers, bogs, ponds, lakes, rivers and streams, and underground as groundwater in aquifers and underground streams. Fresh water is generally characterized by having low concentrations of dissolved salts and other total dissolved solids. The term specifically excludes seawater and brackish water but it does include mineral rich waters such as chalybeate springs. The term "sweet water" has been used to describe fresh water in contrast to salt water.

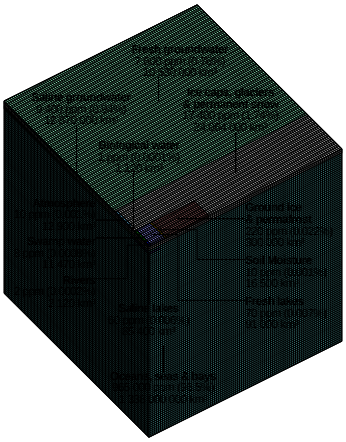

Figure: **Distribution (by volume) of water on Earth**: Visualization of the distribution (by volume) of water on Earth. Each tiny cube (such as the one representing biological water) corresponds to approximately 1000 km³ of water, with a mass of about 1 trillion tonnes (200000 times that of the Great Pyramid of Giza). The entire block comprises 1 million tiny cubes.

Scientifically, freshwater habitats are divided into lentic systems, which are the stillwaters including ponds, lakes, swamps and mires; lotic systems, which are running water; and groundwater which flows in rocks and aquifers. There is, in addition, a zone which bridges between groundwater and lotic systems – the hyporheic zone – which underlies many larger rivers and can contain substantially more water than is seen in the open channel. It may also be in direct contact with the underlying underground water.

Fresh water creates a hypotonic environment for aquatic organisms. This is problematic for some organisms with pervious skins or with gill membranes, whose cell membranes may burst if excess water is not excreted. Some protists accomplish this using contractile vacuoles, while freshwater fish excrete excess water via the kidney. Although most aquatic organisms have a limited ability to regulate their osmotic balance and therefore can only live within a narrow range of salinity, diadromous fish have the

ability to migrate between fresh water and saline water bodies. During these migrations they undergo changes to adapt to the surroundings of the changed salinities; these processes are hormonally controlled. The eel (Anguilla anguilla) uses the hormone prolactin, while in salmon (Salmo salar) the hormone cortisol plays a key role during this process.

Many sea birds have special glands at the base of the bill through which excess salt is excreted. Similarly the marine iguanas on the Galápagos Islands excrete excess salt through a nasal gland and they sneeze out a very salty excretion.

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SECTION OVERVIEW

16.4: Nutrient Cycles

Topic hierarchy

16.4A: Sources and Sinks of Essential Elements

16.4B: The Carbon Cycle

16.4C: Syntrophy and Methanogenesis

16.4D: The Phosphorus Cycle

16.4E: The Nitrogen Cycle

16.4F: The Sulfur Cycle

16.4G: The Iron Cycle

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16.4A: Sources and Sinks of Essential Elements

Biogeochemical cycles are pathways by which essential elements flow from the abiotic and biotic compartments of the Earth.

Learning Objectives

- Identify sources and sinks of essential elements

Key Points

- Biogeochemical cycles are pathways by which nutrients flow between the abiotic and abiotic compartments of the Earth. The abiotic portion of the Earth includes the lithosphere (the geological component of the Earth) and the hydrosphere (the Earth's water).
- Ecosystems rely on biogeochemical cycles. Many of the nutrients that living things depend on, such as carbon, nitrogen, and phosphorous are in constant circulation.
- Essential elements are often stored in reservoirs, where they can be taken out of circulation for years. For example, coal is a reservoir for carbon.
- Humans can affect biogeochemical cycles. Humans extract carbon and nitrogen from the geosphere and use them for energy and fertilizer. This has increased the amount of these elements in circulation, which has detrimental effects on ecosystems.

Key Terms

- **Reservoir**: Reservoirs are places where essential elements are sequestered for long periods of time.
- **biogeochemical cycle**: A pathway by which a chemical element or molecule moves through both biotic (biosphere) and abiotic (lithosphere, atmosphere, and hydropshere) compartments of the planet.

Most important substances on Earth, such as oxygen, nitrogen, and water undergo turnover or cycling through both the biotic (living) and abiotic (geological, atmospheric, and hydrologic) compartments of the Earth. Flows of nutrients from living to non-living components of the Earth are called biogeochemical cycles.

Nutrient Cycles and the Biosphere

Ecosystems hinge on biogeochemical cycles. The nitrogen cycle, the phosphorous cycle, the sulfur cycle, and the carbon cycle all involve assimilation of these nutrients into living things. These elements are transferred among living things through food webs, until organisms ultimately die and release them back into the geosphere.

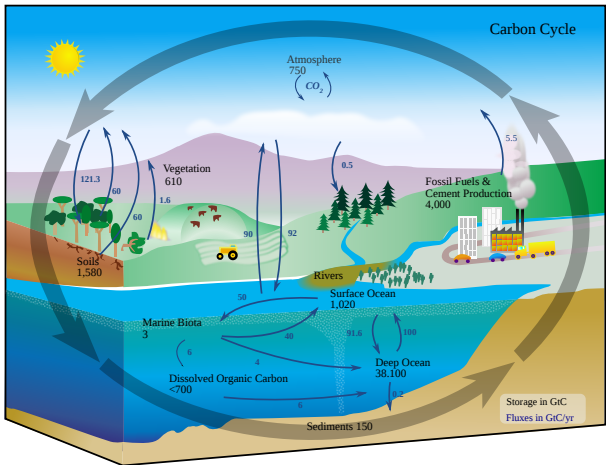

Figure: **The Carbon Cycle**: The element carbon moves from the biosphere to the geosphere and the hydrosphere. This flow from abiotic to biotic compartments of the Earth is typical of biogeochemical cycles.

Reservoirs of Essential Elements

Chemicals are sometimes sequestered for long periods of time and taken out of circulation. Locations where elements are stored for long periods of time are called reservoirs. Coal is a reservoir for carbon, and coal deposits can house carbon for thousands of years. The atmosphere is considered a reservoir for nitrogen.

Humans and Biogeochemical Cycles

Although the Earth receives energy from the Sun, the chemical composition of the planet is more or less fixed. Matter is occasionally added by meteorites, but supplies of essential elements generally do not change. However, human activity can change the proportion of nutrients that are in reservoirs and in circulation. For example, coal is a resevoir of carbon, but the human use of fossil fuels has released carbon into the atmosphere, increasing the amount of carbon in circulation. Likewise, phosphorous and nitrogen are extracted from geological reservoirs and used in phosphorous, and excesses of these elements have caused the overgrowth of plant matter and the disruption of many ecosystems.

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16.4B: The Carbon Cycle

The carbon cycle describes the flow of carbon from the atmosphere to the marine and terrestrial biospheres, and the earth's crust.

Learning Objectives

- Outline the flow of carbon through the biosphere and abiotic matter on earth

Key Points

- Atmospheric carbon is usually in the form of CO_2. Carbon dioxide is converted to organic carbon through photosynthesis by primary producers such as plants, bacteria, and algae.
- Some organic carbon is returned to the atmosphere as CO_2 during respiration. The rest of the organic carbon may cycle from organism to organism through the food chain. When an organism dies, it is decomposed by bacteria and its carbon is released into the atmosphere or the soil.
- Carbon is also found in the earth's crust, primarily as limestone and kerogens.

Key Terms

- **lithosphere**: The rigid, mechanically strong, outer layer of the earth; divided into twelve major tectonic plates.
- **chemoautotrophic**: An organism obtaining its nutrition through the oxidation of non-organic compounds (or other chemical processes); as opposed to the process of photosynthesis.
- **carbon cycle**: The physical cycle of carbon through the Earth's biosphere, geosphere, hydrosphere and atmosphere that includes such processes as photosynthesis, decomposition, respiration and carbonification.

The carbon cycle describes the flow of carbon between the biosphere, the geosphere, and the atmosphere, and is essential to maintaining life on earth.

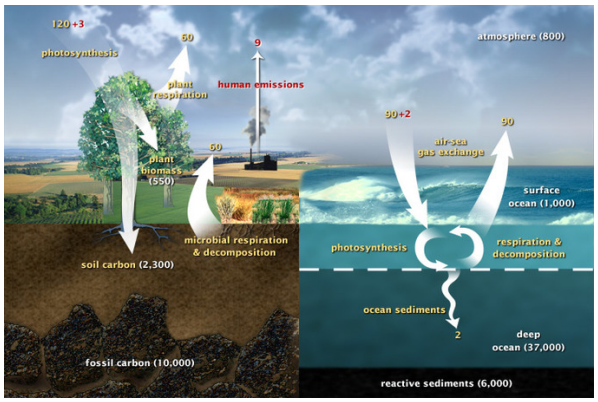


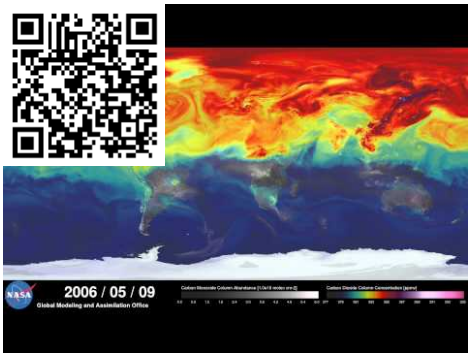
Figure: **The Carbon Cycle**: The carbon cycle describes the flow of carbon between the atmosphere, the biosphere, and the geosphere.

Atmospheric Carbon Dioxide: Carbon in the earth's atmosphere exists in two main forms: carbon dioxide and methane. Carbon dioxide leaves the atmosphere through photosynthesis, thus entering the terrestrial and marine biospheres. Carbon dioxide also dissolves directly from the atmosphere into bodies of water (oceans, lakes, etc.), as well as dissolving in precipitation as raindrops fall through the atmosphere. When dissolved in water, carbon dioxide reacts with water molecules and forms carbonic acid, which contributes to ocean acidity. Human activity over the past two centuries has significantly increased the amount of carbon in the atmosphere, mainly in the form of carbon dioxide, both by modifying ecosystems ' ability to extract carbon dioxide from the atmosphere and by emitting it directly, e.g. by burning fossil fuels and manufacturing concrete.

Terrestrial Biosphere: The terrestrial biosphere includes the organic carbon in all land-living organisms, both alive and dead, as well as carbon stored in soils. Although people often imagine plants as the most important part of the terrestrial carbon cycle, microorganisms such as single celled algae and chemoautotrophic bacteria are also important in converting atmospheric CO_2 into terrestrial carbon. Carbon is incorporated into living things as part of organic molecules, either through photosynthesis or by animals that consume plants and algae. Some of the carbon in living things is released through respiration, while the rest remains in the tissue. Once organisms die, bacteria break down their tissues, releasing CO_2 back into the atmosphere or into the soil.

Marine Biosphere: The carbon cycle in the marine biosphere is very similar to that in the terrestrial ecosystem. CO_2 dissolves in the water and algae, plants and bacteria convert it into organic carbon. Carbon may transfer between organisms (from producers to consumers). Their tissues are ultimately broken down by bacteria and CO_2 is released back into the ocean or atmosphere.

NASA | A Year in the Life of Earth's CO2: An ultra-high-resolution NASA computer model has given scientists a stunning new look at how carbon dioxide in the atmosphere travels around the globe. Plumes of carbon dioxide in the simulation swirl and shift as winds disperse the greenhouse gas away from its sources. The simulation also illustrates differences in carbon dioxide levels in the northern and southern hemispheres and distinct swings in global carbon dioxide concentrations as the growth cycle of plants and trees changes with the seasons. The carbon dioxide visualization was produced by a computer model called GEOS-5, created by scientists at NASA Goddard Space Flight Center's Global Modeling and Assimilation Office. The visualization is a product of a simulation called a "Nature Run." The Nature Run ingests real data on atmospheric conditions and the emission of greenhouse gases and both natural and man-made particulates. The model is then left to run on its own and simulate the natural behavior of the Earth's atmosphere. This Nature Run simulates January 2006 through December 2006. While Goddard scientists worked with a "beta" version of the Nature Run internally for several years, they released this updated, improved version to the scientific community for the first time in the fall of 2014.



Geologic Carbon: The earth's crust also contains carbon. Much of the earth's carbon is stored in the mantle, and has been there since the earth formed. Much of the carbon on the earth's lithosphere (about 80%) is stored in limestone, which was formed from the calcium carbonate from the shells of marine animals. The rest of the carbon on the earth's surface is stored in Kerogens, which were formed through the sedimentation and burial of terrestrial organisms under high heat and pressure.

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16.4C: Syntrophy and Methanogenesis

Bacteria that perform anaerobic fermentation often partner with methanogenic archea bacteria to provide necessary products such as hydrogen.

Learning Objectives

- Assess syntrophy methanogenesis

Key Points

- Methanogenic bacteria are only found in the domain Archea, which are bacteria with no nucleus or other organelles.
- Methanogenesis is a form of respiration in which carbon rather than oxygen is used as an electron acceptor.
- Bacteria that perform anaerobic fermentation often partner with methanogenic bacteria. During anaerobic fermentation, large organic molecules are broken down into hydrogen and acetic acid, which can be used in methanogenic respiration.
- There are other examples of syntrophic relationships between methanogenic bacteria and mircoorganisms: protozoans in the guts of termites break down cellulose and produce hydrogen which can be used in methanogenesis.

Key Terms

- **Archea**: A domain of single-celled microorganisms. These microbes have no cell nucleus or any other membrane-bound organelles within their cells.
- **syntrophy**: A phenomenon where one species lives off the products of another species.
- **methanogenesis**: The generation of methane by anaerobic bacteria.

Syntrophy or cross feeding is when one species lives off the products of another species. A frequently cited example of syntrophy are methanogenic archaea bacteria and their partner bacteria that perform anaerobic fermentation.



Figure: **Methanogenic Bacteria in Termites**: Methanogenic bacteria have a syntrophic relationship with protozoans living in the guts of termites. The protozoans break down cellulose, releasing H2 which is then used in methanogenesis.

Methanogenesis in microbes is a form of anaerobic respiration, performed by bacteria in the domain Archaea. Unlike other microorganisms, methanogens do not use oxygen to respire; but rather oxygen inhibits the growth of methanogens. In methanogenesis, carbon is used as the terminal electron receptor instead of oxygen. Although there are a variety of potential carbon based compounds that are used as electron receptors, the two best described pathways involve the use of carbon dioxide and acetic acid as terminal electron acceptors.

Acetic Acid: $CO2+4H2 \rightarrow CH4+2H2OCO2+4H2 \rightarrow CH4+2H2O$

Carbon Dioxide: $CH3COOH \rightarrow CH4+CO2CH3COOH \rightarrow CH4+CO2$

Many methanogenic bacteria that live in close association with bacteria produce fermentation products such as fatty acids longer than two carbon atoms, alcohols longer than one carbon atom, and branched chain and aromatic fatty acids. These products cannot be used in methanogenesis. Partner bacteria of the methanogenic archea therefore process these products. By oxydizing them to acetate, they allow them to be used in methanogenesis.

Methanogenic bacteria are important in the decomposition of biomass in most ecosystems. Only methanogenesis and fermentation can occur in the absence of electron acceptors other than carbon. Fermentation only allows the breakdown of larger organic compounds, and produces small organic compounds that can be used in methanogenesis. The semi-final products of decay (hydrogen, small organics, and carbon dioxide) are then removed by methanogenesis. Without methanogenesis, a great deal of carbon (in the form of fermentation products) would accumulate in anaerobic environments.

Methanogenic archea bacteria can also form associations with other organisms. For example, they may also associate with protozoans living in the guts of termites. The protozoans break down the cellulose consumed by termites, and release hydrogen, which is then used in methanogenesis.

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16.4D: The Phosphorus Cycle

Phosphorus, important for creating nucleotides and ATP, is assimilated by plants, then released through decomposition when they die.

Learning Objectives

- Explain the phosphorous cycle

Key Points

- Phosphorous is important for the production of ATP and nucleotides.
- Inorganic phosphorous is found in the soil or water. Plants and algae assimilate inorganic phosphorus into their cells, and transfer it to other animals that consume them.
- When organisms die, their phosphorous is released by decomposer bacteria.
- Aquatic phosphorous follows a seasonal cycle, inorganic phosphorous peaks in the spring causing rapid algae and plant growth, and then declines. As plants die, it is re-released into the water.
- Phosphorous based fertilizers can cause excessive algae growtin in aquatic systems, which can have negative impacts on the environment.

Key Terms

- **hypertrophication**: the ecosystem response to the addition of artificial or natural substances, such as nitrates and phosphates, through fertilizers or sewage, to an aquatic system. This response is usually an increase in primary production.

Phosphorus is an important element for living things because it is neccesary for nucleotides and ATP. Plants assimilate phosphorous from the environment and then convert it from inorganic phosphorous to organic phosphorous. Phosphorous can be transfered to other organisms when they consume the plants and algae. Animals either release phosphorous through urination or defecation, when they die and are broken down by bacteria. The organic phosphorous is released and converted back into inorganic phosphorous through decomposition. The phosphorous cycle differs from other nutrient cycles, because it never passes through a gaseous phase like the nitrogen or carbon cycles.

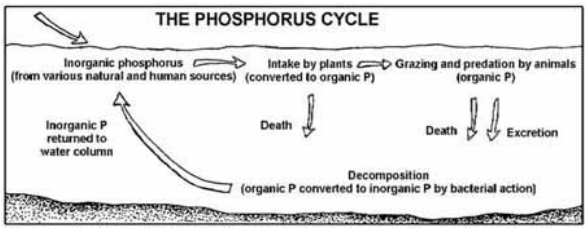

Figure: **The aquatic phosphorous cycle**: Phosphorous is converted between its organic and inorganic forms. Plants convert phosphorous to its organic form, and bacteria convert it back to the inorganic form through decomposition

Phosphorous levels follow a seasonal pattern in aquatic ecosystems. In the spring, inorganic phosphorous is released from the sediment by convection currents in the warming water. When phosphorous levels are high, algae and plants reproduce rapidly. Much of the phosphorous is then converted to organic phosphorous, and primary productivity then declines. Later in the summer, the plants and algae begin to die off, and bacteria decompose them, and inorganic phosphorus is released back into the ecosystem. As phosphorous levels begin to increase at the end of the summer, primary plants and algae begin to rapidly grow again.

The phosphorous cycle is affected by human activities. Although phosphorous is normally a limiting nutrient, most agricultural fertilizers contain phosphorous. Run-off and drainage from farms can flood aquatic ecosystems with excess phosphorus. Artificial phosphorous can cause over growth of algae and plants in aquatic ecosytems. When the excess plant material is broken down, the decomposing bacteria can use up all the oxygen in the water causing dead zones. Most bodies of water gradually become more productive over time through the slow, natural accumulation of nutrients in a process called eutrophication. However, overgrowth of algae due to phosphorous fertilizer is called “cultural eutrophication” or “hypertrophication,” and is generally negative for ecosystems.

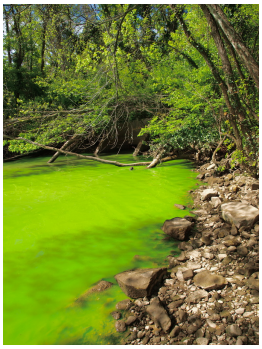

Figure: **Hypertrophication on the Potomac River**: The bright green color of the water is the result of algae blooms in response to the addition of phosphorous based fertilizers.

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16.4E: The Nitrogen Cycle

The nitrogen cycle is the process by which nitrogen is converted from organic to inorganic forms; many steps are performed by microbes.

Learning Objectives

- Describe the nitrogen cycle and how it is affected by human activity

Key Points

- Nitrogen is converted from atmospheric nitrogen (N2) into usable forms, such as NO2-, in a process known as fixation. The majority of nitrogen is fixed by bacteria, most of which are symbiotic with plants.
- Recently fixed ammonia is then converted to biologically useful forms by specialized bacteria. This occurs in two steps: first, bacteria convert ammonia in to (nitrites) NO2-, and then other bacteria species convert it to NO3- (nitrate).
- Nitriates are a form of nitrogen that is usable by plants. It is assimilated into plant tissue as protein. The nitrogen is passed through the food chain by animals that consume the plants, and then released into the soil by decomposer bacteria when they die.
- De-nitrifying bacteria convert NO2- back into atmospheric nitrogen (N2), completing the cycle.

Key Terms

- **de-nitrification**: A microbially facilitated process of nitrate reduction that may ultimately produce molecular nitrogen (N2) through a series of intermediate gaseous nitrogen oxide products.
- **nitrification**: The biological oxidation of ammonia with oxygen into nitrite followed by the oxidation of these nitrites into nitrates.
- **ammonification**: The formation of ammonia or its compounds from nitrogenous compounds, especially as a result of bacterial decomposition.

The nitrogen cycle describes the conversion of nitrogen between different chemical forms. The majority of the earth's atmosphere (about 78%) is composed of atmospheric nitrogen, but it is not in a form that is usable to living things. Complex species interactions allow organisms to convert nitrogen to usable forms and exchange it between themselves. Nitrogen is essential for the formation of amino acids and nucleotides. It is essential for all living things.

Fixation: In order for organisms to use atmospheric nitrogen (N_2), it must be "fixed" or converted into ammonia (NH_3). This can happen occasionally through a lightning strike, but the bulk of nitrogen fixation is done by free living or symbiotic bacteria. These bacteria have the nitrogenase enzyme that combines gaseous nitrogen with hydrogen to produce ammonia. It is then further converted by the bacteria to make their own organic compounds. Some nitrogen fixing bacteria live in the root nodules of legumes where they produce ammonia in exchange for sugars. Today, about 30% of the total fixed nitrogen is manufactured in chemical plants for fertilizer.

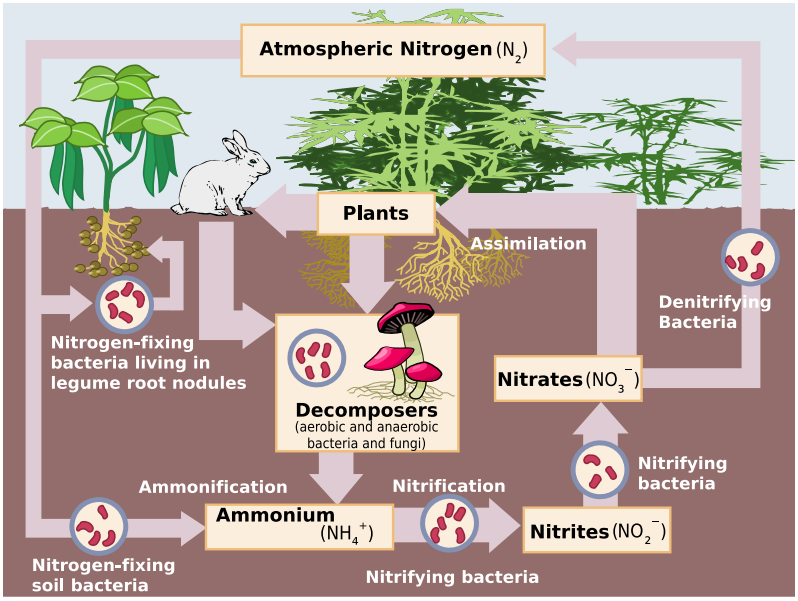

Figure: **The role of soil bacteria in the Nitrogen cycle**: Nitrogen transitions between various biologically useful forms.

Nitrificaton: Nitrification is the conversion of ammonia (NH_3) to nitrate (NO_3^-). It is usually performed by soil living bacteria, such as nitrobacter. This is important because plants can assimilate nitrate into their tissues, and they rely on bacteria to convert it from ammonia to a usable form. Nitrification is performed mainly by the genus of bacteria, *Nitrobacter*.

Ammonification /Mineralization: In ammonification, bacteria or fungi convert the organic nitrogen from dead organisms back into ammonium (NH_4^+). Nitrification can also work on ammonium. It can either be cycled back into a plant usable form through nitrification or returned to the atmosphere through de-nitrification.

De-Nitrification: Nitrogen in its nitrate form (NO_3^-) is converted back into atmospheric nitrogen gas (N_2) by bacterial species such as Pseudomonas and Clostridium, usually in anaerobic conditions. These bacteria use nitrate as an electron acceptor instead of oxygen during respiration.

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16.4F: The Sulfur Cycle

Many bacteria can reduce sulfur in small amounts, but some bacteria can reduce sulfur in large amounts, in essence, breathing sulfur.

Learning Objectives

- Describe the sulfur cycle

Key Points

- The sulfur cycle describes the movement of sulfur through the geosphere and biosphere. Sulfur is released from rocks through weathering, and then assimilated by microbes and plants. It is then passed up the food chain and assimilated by plants and animals, and released when they decompose.
- Many bacteria can reduce sulfur in small amounts, but some specialized bacteria can perform respiration entirely using sulfur. They use sulfur or sulfate as an electron receptor in their respiration, and release sulfide as waste. This is a common form of anaerobic respiration in microbes.
- Sulfur reducing pathways are found in many pathogenic bacteria species. Tuberculosis and leprosy are both caused by bacterial species that reduce sulfur, so the sulfur reduction pathway is an important target of drug development.

Key Terms

- **extremophile**: An organism that lives under extreme conditions of temperature, salinity, and so on. They are commercially important as a source of enzymes that operate under similar conditions.
- **assimilatory sulfate reduction**: The reduction of 3′-Phosphoadenosine-5′-phosphosulfate, a more elaborated sulfateester, leads also to hydrogen sulfide, the product used in biosynthesis (e.g., for the production of cysteine because the sulfate sulfur is assimilated).

The Sulfur Cycle

The sulfur cycle describes the movement of sulfur through the atmosphere, mineral forms, and through living things. Although sulfur is primarily found in sedimentary rocks or sea water, it is particularly important to living things because it is a component of many proteins.

Sulfur is released from geologic sources through the weathering of rocks. Once sulfur is exposed to the air, it combines with oxygen, and becomes sulfate SO_4. Plants and microbes assimilate sulfate and convert it into organic forms. As animals consume plants, the sulfur is moved through the food chain and released when organisms die and decompose.

Some bacteria – for example Proteus, Campylobacter, Pseudomonas and Salmonella – have the ability to reduce sulfur, but can also use oxygen and other terminal electron acceptors. Others, such as Desulfuromonas, use only sulfur. These bacteria get their energy by reducing elemental sulfur to hydrogen sulfide. They may combine this reaction with the oxidation of acetate, succinate, or other organic compounds.

The most well known sulfur reducing bacteria are those in the domain Archea, which are some of the oldest forms of life on Earth. They are often extremophiles, living in hot springs and thermal vents where other organisms cannot live. Lots of bacteria reduce small amounts of sulfates to synthesize sulfur-containing cell components; this is known as assimilatory sulfate reduction. By contrast, the sulfate-reducing bacteria considered here reduce sulfate in large amounts to obtain energy and expel the resulting sulfide as waste. This process is known as dissimilatory sulfate reduction. In a sense, they breathe sulfate.

Sulfur metabolic pathways for bacteria have important medical implications. For example, Mycobacterium tuberculosis (the bacteria causing tuberculosis) and Mycobacterium leprae (which causes leoprosy) both utilize sulfur, so the sulfur pathway is a target of drug development to control these bacteria.

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16.4G: The Iron Cycle

Iron is an important limiting nutrient required for plants and animals; it cycles between living organisms and the geosphere.

Learning Objectives

- Compare the terrestrial and marine iron cycles

Key Points

- Iron is an important limiting nutrient for plants, which use it to produce chlorophyll. Photosynthesis depends on adequate iron supply. Plants assimilate iron from the soil into their roots.
- Animals consume plants and use the iron to produce hemoglobin, the oxygen transports protein found in red blood cells. When animals die, decomposing bacteria return iron to the soil.
- The marine iron cycle is very similar to the terrestrial iron cycle, except that phytoplankton and cyanobacteria assimilate iron.
- Iron fertilization has been studied as a method for sequestering carbon. Scientists have hoped that by adding iron to the ocean, plankton might be able to sequester the excess CO_2 responsible for climate change. However, there is concern about the long term effects of this strategy.

Key Terms

- **hemoglobin**: the iron-containing oxygen transport metalloprotein in the red blood cells of all vertebrates

Iron (Fe) follows a geochemical cycle like many other nutrients. Iron is typically released into the soil or into the ocean through the weathering of rocks or through volcanic eruptions.

The Terrestrial Iron Cycle: In terrestrial ecosystems, plants first absorb iron through their roots from the soil. Iron is required to produce chlorophyl, and plants require sufficient iron to perform photosynthesis. Animals acquire iron when they consume plants, and iron is utilized by vertebrates in hemoglobin, the oxygen-binding protein found in red blood cells. Animals lacking in iron often become anemic and cannot transmit adequate oxygen. Bacteria then release iron back into the soil when they decompose animal tissue.

The Marine Iron Cycle: The oceanic iron cycle is similar to the terrestrial iron cycle, except that the primary producers that absorb iron are typically phytoplankton or cyanobacteria. Iron is then assimilated by consumers when they eat the bacteria or plankton. The role of iron in ocean ecosystems was first discovered when English biologist Joseph Hart noticed “desolate zones,” which are regions that lacked plankton but were rich in nutrients. He hypothesized that iron was the limiting nutrient in these areas. In the past three decades there has been research into using iron fertilization to promote alagal growth in the world’s oceans. Scientists hoped that by adding iron to ocean ecosystems, plants might grown and sequester atmospheric CO_2. Iron fertilization was thought to be a possible method for removing the excess CO_2 responsible for climate change. Thus far, the results of iron fertilization experiments have been mixed, and there is concern among scientists about the possible consequences of tampering nutrient cycles.

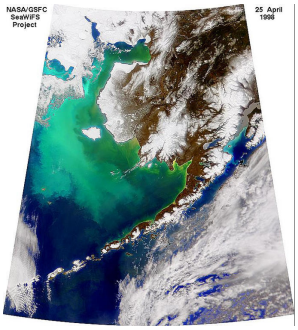

Figure: **Algal bloom**: Algae bloom in the Bering Sea after a natural iron fertilization event.

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SECTION OVERVIEW

16.5: Microbial Symbioses

Topic hierarchy

16.5A: Mutualism vs. Symbiosis

16.5B: The Rumen and Ruminant Animals

16.5C: Hydrothermal Vent Microbial Ecosystems

16.5D: Squid-Aliivibrio Symbiosis

16.5E: Mutualistic Relationships with Fungi and Fungivores

16.5F: Agrobacterium and Crown Gall Disease

16.5G: The Legume-Root Nodule Symbiosis

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16.5A: Mutualism vs. Symbiosis

Symbiosis is a relationship between two organisms: it can be mutualistic (both benefit), commensal (one benefits), or parasitic.

Learning Objectives

- Compare Mutualism and Symbiosis

Key Points

- Mutualism, a relationship in which both species benefit, is common in nature. In microbiology, there are many examples of mutualistic bacteria in the gut that aid digestion in both humans and animals.
- Commensalism is a relationship between species in which one benefits and the other is unaffected. Humans are host to a variety of commensal bacteria in their bodies that do not harm them but rely on them for survival (e.g. bacteria that consume dead skin).
- Parasitic relationships, in which one species benefits and the other suffers, are very common in nature. Most of the microorganisms studied in medical microbiology are parasitic and feed on human tissue. For example, cholera, leshmaniasis, and Giardia are all parasitic microbes.
- Symbiotic relationships can also be classified by the physical relationship between the two species. Endosymbionts live inside the tissues of the host, while ectosymbionts live outside of their partner species.

Key Terms

- **commensalism**: A class of relationship between two organisms in which one organism benefits without affecting the other
- **symbiosis**: A close and often long-term interaction between two or more different biological species
- **mutualism**: A relationship between individuals of different species in which both individuals benefit

Symbiosis is any relationship between two or more biological species. Such relationships are usually long term and have a strong impact on the fitness of one or both organisms. Symbiotic relationships are categorized by the benefits and physical relationships experienced by each species.

Common types of symbiosis are categorized by the degree to which each species benefits from the interaction:

- Mutualism: In mutualistic interactions, both species benefit from the interaction. A classic example of mutualism is the relationship between insects that pollinate plants and the plants that provide those insects with nectar or pollen. Another classic example is the behavior of mutualistic bacteria in ecology and human health. Gut bacteria in particular are very important for digestion in humans and other species. In humans, gut bacteria assist in breaking down additional carbohydrates, out-competing harmful bacteria, and producing hormones to direct fat storage. Humans lacking healthy mutualistic gut flora can suffer a variety of diseases, such as irritable bowel syndrome. Some ruminant animals, like cows or deer, rely on special mutualistic bacteria to help them break down the tough cellulose in the plants they eat. In return, the bacteria get a steady supply of food.
- Commensalism: In commensalism, one organism benefits while the other organism neither benefits nor suffers from the interaction. For example, a spider may build a web on a plant and benefit substantially, while the plant remains unaffected. Similarly, a clown fish might live inside a sea anemone and receive protection from predators, while the anemone neither benefits nor suffers.
- Parasitism: Parasites are organisms that harm their symbiotic partners. Parasitism is incredibly common in nature: depending on the definition, more than half of all species may go through at least one parasitic stage in their life cycle. There are many well-documented examples of parasitic bacteria and microorganisms throughout this text.

Symbiosis can also be characterized by an organism's physical relationship with its partner.

- Endosymbiosis: a relationship in which one of the symbiotic species lives inside the tissue the other. For example, Coral polyps have special algae called zooxanthelle that live inside their cells. Zooxanthelle provide sugars to the coral through photosynthesis. Similarly, nitrogen-fixing fungi often live inside the cells of plants, providing nitrogen in exchange for the sugars of photosynthesis.
- Ectosymbiosis: a relationship in which one species lives on the outside surface of the other. Barnacles that live on whales and bromeliads that live on tropical trees are examples of endosymbionts.

These categories can be paired with the above terms to better describe the species' interactions. For example, you might say that a gut bacteria is an "endosymbiotic mutualist," or that a flea is an "ectosymbiotic parasite. "

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16.5B: The Rumen and Ruminant Animals

Ruminant animals (such as deer and cows) digest food in a four-chambered stomach with the help of special bacteria, protozoa, and fungi.

Learning Objectives

- Identify how ruminant animals host symbiotic bacteria

Key Points

- Ruminant animals use a special four-chambered stomach with a unique microbial flora to digest tough cellulose found in the plants in their diets. Most vertebrates cannot make cellulase, the enzyme that breaks down cellulose, but microbes in the rumen produce it for them.
- Ruminants chew and ingest plant matter and then swallow it. The plant matter is separated into liquids and solids in the rumen, and liquids drain into the reticulum. Solids in the rumen are then regurgitated into the mouth to be chewed and further broken down.
- Liquids pass from the reticulum into the omasum, where sugars, fatty acids, and other nutrients are absorbed into the blood stream.
- After the omasum, food passes into the abomasum, which is much like the stomach in non-ruminant (monogastric) animals, and from there moves into the small intestine, where it is digested.

Key Terms

- **Rumen**: The first chamber in the alimentary canal of ruminant animals. It serves as the primary site for microbial fermentation of ingested feed.
- **Abomasum**: The fourth and final stomach compartment in ruminants. It secretes rennin – the artificial form of which is called rennet, and is used in cheese creation.
- **Omasum**: The third compartment of the stomach in ruminants. Though its functions have not been well-studied, it appears to primarily aid in the absorption of water, magnesium, and the volatile fatty acids produced.

A Ruminant's Multi-chambered Stomach

Ruminants are mammals that digest plant based food by processing it in a series of chambers in their stomachs. There are about 150 species of ruminants, including both domestic and wild species. Ruminating mammals include cattle, goats, sheep, giraffes, bison, moose, elk, yaks, water buffalo, deer, camels, alpacas, llamas, and antelope.

Ruminants differ from non-ruminants (called monogastrics) because they have a four-chambered stomach. The four compartments are called the rumen, the reticulum, the omasum, and the abomasum. The rumen and the reticulum are connected and work in concert and are therefore sometimes called the "reticulorumen".

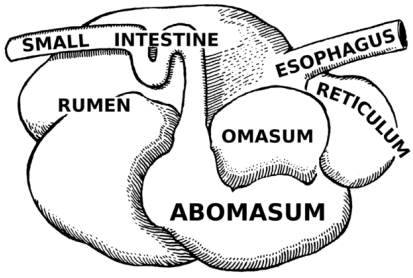

Figure: **The digestive tract of a ruminant**: The ruminant digestive tract has four compartments, the rumen, the reticulum, the omasum, and abomasum.

The Ruminant Digestive Process

- Ruminants chew plant matter to mix it with saliva and swallow. The food then enters the first two stomach chambers, the reticulum and rumen (or reticulorumen).

- The reticulum and rumen work together to separate solids and liquids. Contractions push solid food particles back up into the rumen, while liquids are drained into the reticulum. Specialized microbe species live in the rumen and help ruminants break down cellulose.
- Solids are formed into a bolus, called “cud,” in the rumen and the solid cud is regurgitated back up to the mouth where it is chewed a second time, and returned to the reticulorumen to repeat the process.
- Liquid digesta in the reticulum is passed into the omasum where nutrients and water are absorbed into the blood stream.
- After this, digesta is passed into the abomasum, which is similar to the stomach of other animals. After the abomasum, digesta moves through the large and small intestines.

Ruminants are of interest to microbiologists because they have unique species of bacteria, yeasts, protozoa, and fungi in their rumens. The plant matter consumed by ruminants is high in cellulose, but vertebrates cannot produce cellulase which is the enzyme required to break down cellulose. Thus ruminants depend on the symbiotic microbes in their guts to break down cellulose for digestion. There is no oxygen in the rumen, so bacteria in the rumen are typically anaerobes or facultative anaerobes.

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16.5C: Hydrothermal Vent Microbial Ecosystems

Hydrothermal vents are home to chemosynthetic bacteria, which are the basis of a unique ecosystem that thrives in total darkness.

Learning Objectives

- Describe hydrothermal vent microbial ecosystems

Key Points

- Hydrothermal vents emit nutrient rich, geothermally heated water. Mats of chemosynthetic bacteria grow around the vents and synthesize carbohydrates from the carbon dioxide ejected by the vent.
- Many species of crabs, worms, snails, and tube worms depend on these bacterial mats for food. These species are often specially adapted to life in the lightless, high pressure, and hot environment of the vent.
- Vents are the target of exploitation of the mining industry, which is a cause for concern among marine biologists. Mining could damage these very unique and diverse ecosystems.

Key Terms

- **chemosynthesis**: The production of carbohydrates and other compounds from simple compounds such as carbon dioxide, using the oxidation of chemical nutrients as a source of energy rather than sunlight; it is limited to certain bacteria and fungi.
- **geothermal**: Pertaining to heat energy extracted from reservoirs in the earth's interior.

Hydrothermal Vents and Their Microbial Communities

A hydrothermal vent is a fissure in the earth's surface from which geothermally heated water issues. They are typically found deep below the surface of the ocean. Hydrothermal vents are of interest to microbiologists because they have unique microbial communities found nowhere else on earth.

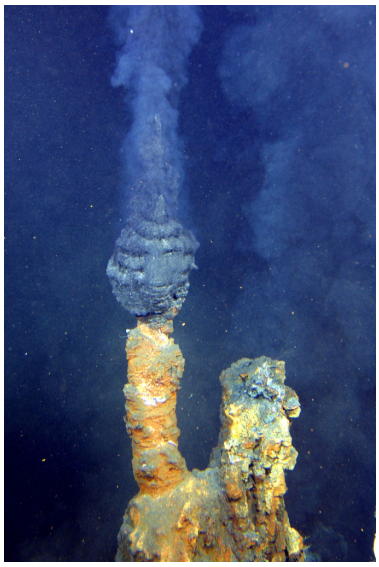

Figure: **Hydrothermal Vents**: Hydrothermal vents are cracks in the earth's crust where geothermally heated water leaks out.

In most shallow water and terrestrial ecosystems, energy comes from sunlight, but in the deep ocean there is total darkness. However, hydrothermal vents often expel nutrient rich water, containing methane and sulfur compounds. Vent bacteria can synthesize all the compounds they need to live from these nutrients, a process called chemosynthesis. These bacteria form the basis of the entire hydrothermal vent ecosystem.

The chemosynthetic bacteria grow into a thick mat, covering the hydrothermal vent, and this is the first trophic level of the ecosystem. Snails, shrimp crabs, tube worms, and fish feed on the bacterial mat and attract larger organisms such as squid and octopuses. Many of these species are specially adapted to live in the dark and lack eyes. Hydrothermal vents are biodiversity hot spots because they have many species that are uniquely adapted to live in this harsh environment. For example, the Pompeii tube

worm *Alvinella pompejana* can resist temperatures up to 176°F. These ecosystems are almost entirely independent of sunlight (although the dissolved oxygen used by some animals does ultimately come from plants at the surface).

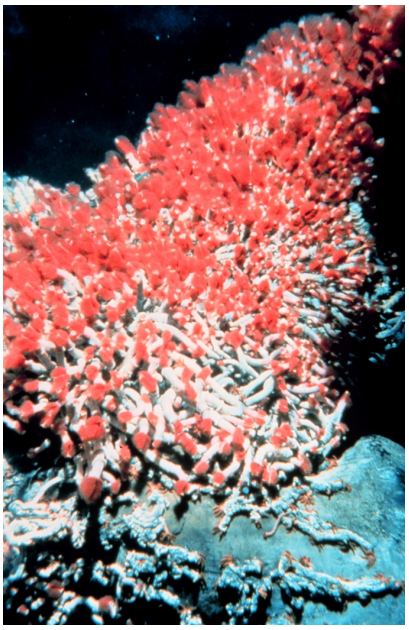

Figure: **Tubeworms Living Near A Hydrothermal Vent**: Some species of tube worms are specially adapted to withstand the high temperatures found at hydrothermal vents.



Figure: **Crabs near a hydrothermal vent**: The ecosystems around hydrothermal vents rely on mats chemosynthetic bacteria, and many species feed on the bacteria. Hydrothermal vents are some of the most unique ecosystems in the world

Despite being some of the most remote ecosystems in the world, hydrothermal vents are under threat from mining companies. As mineral resources on land have become depleted, mining companies have turned to deep sea geothermal vents to extract metals and sulfur. Although the technology for deep sea mining is new, conservation biologists are concerned that mining hydrothermal vents will destroy these fragile and unique ecosystems.

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16.5D: Squid-Aliivibrio Symbiosis

Squid host light-generating Allivibiro bacteria in a special organ so that they can illuminate themselves and blend in with the environment.

Learning Objectives

- Explain the symbiotic relationship of squid and aliivibrio

Key Points

- Squid rely on Allivibrio bacteria to generate light that allows them to blend in with the light coming from above. Animals below them cannot see their shadow when they view the squid from below.
- Squid use mucus to attract many species of bacteria into their light organ, but they sort out Aliivibiro in several ways. Ciliated cells in the light organ create a current that expels most bacteria, and the squid uses hydrogen peroxide to create a hostile environment that Aliivibrio can resist.
- Once inside the light organ, the Aliivibrio bacteria receive sugars and amino acids from the squid. However, this is costly to the squid, and the squid clears out its light organ during the day so that it does not have to constantly maintain a colony of Aliivibrio bacteria.

Key Terms

- **cilia**: Organelles found in eukaryotic cells. Cilia are slender protuberances that project from the much larger cell body.
- **BIoluminescence**: The emission of light by a living organism.

Bioluminescence

A special category of symbiotic relationships involve bioluminescence, where light producing bacteria are hosted by another organism. One of the best studied examples of bioluminescence is the Hawaiian bobtail squid (*Euprymna scolopes*) and its mutualistic bacteria, *Aliivibrio fischeri*. Aliivibrio fischeri inhabits a special light organ in the squid's mantle. The bacteria are fed a sugar and amino acid solution by the squid. In return, they produce light to hide the squid's silhouette when viewed from below, allowing the squid to match ambient light conditions.



Figure: **Bobtail Squid**: Bobtail squid rely on their mutualist bacteria Allivibrio fischerii to generate light. The bacteria inhabits a special light organ in the squid's mantle and receives sugars and amino acids in exchange for light.

Bobtail squid hatchlings do not have *Aliivibrio fischeri* naturally in their bodies. They are born with a special light organ structure, with cilliated cells at the opening designed to trap passing *A. fischeri*, but must obtain the bacteria from sea water. To do this, the squid secretes a special mucus whenever its cells detect peptidoglycan (which is found in the cell walls of bacteria). The mucus collects near the opening of the light organ which traps passing bacteria. The squid weeds out unwanted bacteria in several ways. For instance, *A. fischeri* is able to survive in the mucus better than other species. It is also a very mobile bacteria, and is able to swim against the current created by the cilia at the mouth of the light organ.

The squid also creates a hostile environment at the entrance to the light organ by secreting an enzyme that splits hydrogen peroxide, creating a toxic environment for most bacteria. *Aliivibrio fischeri* can capture hydrogen peroxide before the squid can use it as a toxin, and thus can survive in the hostile chemical environment. Once *A. fischeri* has passed these hurdles at the opening of the light organ, it can colonize chambers of the light organ and begin enjoying the benefits of symbiosis.

Despite all the effort that goes into obtaining *Aliivibrio fischeri*, the squid ejects 95% of its bacteria every day. It not fully understood why the squid cleans out its light organ, but the bacteria require a great deal of sugar and amino acids, so it may be most useful to the squid to host bacteria only when they are needed. It may also provide a supply of bacteria for squid hatchlings.

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16.5E: Mutualistic Relationships with Fungi and Fungivores

Members of Kingdom Fungi form ecologically beneficial mutualistic relationships with cyanobateria, plants, and animals.

Learning Objectives

- Describe mutualistic relationships with fungi

Key Points

- Mutualistic relationships are those where both members of an association benefit; Fungi form these types of relationships with various other Kingdoms of life.
- Mycorrhiza, formed from an association between plant roots and primitive fungi, help increase a plant's nutrient uptake; in return, the plant supplies the fungi with photosynthesis products for their metabolic use.
- In lichen, fungi live in close proximity with photosynthetic cyanobateria; the algae provide fungi with carbon and energy while the fungi supplies minerals and protection to the algae.
- Mutualistic relationships between fungi and animals involves numerous insects; Arthropods depend on fungi for protection, while fungi receive nutrients in return and ensure a way to disseminate the spores into new environments.

Key Terms

- **mycorrhiza**: a symbiotic association between a fungus and the roots of a vascular plant
- **lichen**: any of many symbiotic organisms, being associations of fungi and algae; often found as white or yellow patches on old walls, etc.
- **thallus**: vegetative body of a fungus

Mutualistic Relationships

Symbiosis is the ecological interaction between two organisms that live together. However, the definition does not describe the quality of the interaction. When both members of the association benefit, the symbiotic relationship is called mutualistic. Fungi form mutualistic associations with many types of organisms, including cyanobacteria, plants, and animals.

Fungi & Plant Mutualism

Mycorrhiza, which comes from the Greek words "myco" meaning fungus and "rhizo" meaning root, refers to the association between vascular plant roots and their symbiotic fungi. About 90 percent of all plant species have mycorrhizal partners. In a mycorrhizal association, the fungal mycelia use their extensive network of hyphae and large surface area in contact with the soil to channel water and minerals from the soil into the plant, thereby increasing a plant's nutrient uptake. In exchange, the plant supplies the products of photosynthesis to fuel the metabolism of the fungus.

Mycorrhizae display many characteristics of primitive fungi: they produce simple spores, show little diversification, do not have a sexual reproductive cycle, and cannot live outside of a mycorrhizal association. There are a number of types of mycorrhizae. Ectomycorrhizae ("outside" mycorrhiza) depend on fungi enveloping the roots in a sheath (called a mantle) and a Hartig net of hyphae that extends into the roots between cells. The fungal partner can belong to the Ascomycota, Basidiomycota, or Zygomycota. In a second type, the Glomeromycete fungi form vesicular–arbuscular interactions with arbuscular mycorrhiza (sometimes called endomycorrhizae). In these mycorrhiza, the fungi form arbuscules that penetrate root cells and are the site of the metabolic exchanges between the fungus and the host plant. The arbuscules (from the Latin for "little trees") have a shrub-like appearance. Orchids rely on a third type of mycorrhiza. Orchids are epiphytes that form small seeds without much storage to sustain germination and growth. Their seeds will not germinate without a mycorrhizal partner (usually a Basidiomycete). After nutrients in the seed are depleted, fungal symbionts support the growth of the orchid by providing necessary carbohydrates and minerals. Some orchids continue to be mycorrhizal throughout their lifecycle.

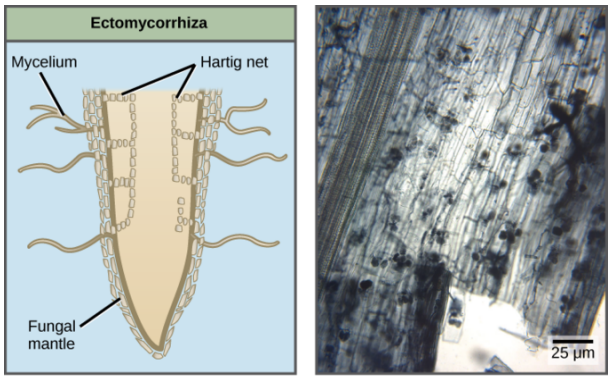

Figure: **Mycorrhizal fungi**: (a) Ectomycorrhiza and (b) arbuscular mycorrhiza have different mechanisms for interacting with the roots of plants.

Lichens

Lichens display a range of colors and textures. They can survive in the most unusual and hostile habitats. They cover rocks, gravestones, tree bark, and the ground in the tundra where plant roots cannot penetrate. Lichens can survive extended periods of drought: they become completely desiccated and then rapidly become active once water is available again. Lichens fulfill many ecological roles, including acting as indicator species, which allow scientists to track the health of a habitat because of their sensitivity to air pollution.

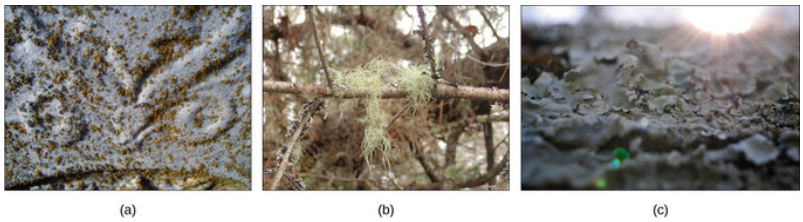

Figure: **Lichen: fungi and cyanobateria**: Lichens have many forms. They may be (a) crust-like, (b) hair-like, or (c) leaf-like.

Lichens are not a single organism, but, rather, an example of a mutualism in which a fungus (usually a member of the Ascomycota or Basidiomycota phyla) lives in close contact with a photosynthetic organism (a eukaryotic alga or a prokaryotic cyanobacterium). Generally, neither the fungus nor the photosynthetic organism can survive alone outside of the symbiotic relationship. The body of a lichen, referred to as a thallus, is formed of hyphae wrapped around the photosynthetic partner. The photosynthetic organism provides carbon and energy in the form of carbohydrates. Some cyanobacteria fix nitrogen from the atmosphere, contributing nitrogenous compounds to the association. In return, the fungus supplies minerals and protection from dryness and excessive light by encasing the algae in its mycelium. The fungus also attaches the symbiotic organism to the substrate.

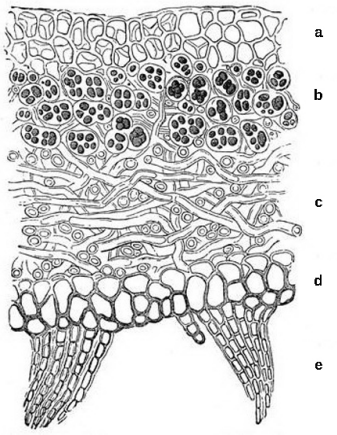

Figure: **Thallus of lichen**: This cross-section of a lichen thallus shows the (a) upper cortex of fungal hyphae, which provides protection; the (b) algal zone where photosynthesis occurs, the (c) medulla of fungal hyphae, and the (d) lower cortex, which also provides protection and may have (e) rhizines to anchor the thallus to the substrate.

The thallus of lichens grows very slowly, expanding its diameter a few millimeters per year. Both the fungus and the alga participate in the formation of dispersal units for reproduction. Lichens produce soredia, clusters of algal cells surrounded by mycelia. Soredia are dispersed by wind and water and form new lichens.

Fungi & Animal Mutualism

Fungi have evolved mutualisms with numerous insects. Arthropods (jointed, legged invertebrates, such as insects) depend on the fungus for protection from predators and pathogens, while the fungus obtains nutrients and a way to disseminate spores into new environments. The association between species of Basidiomycota and scale insects is one example. The fungal mycelium covers and protects the insect colonies. The scale insects foster a flow of nutrients from the parasitized plant to the fungus. In a second example, leaf-cutting ants of Central and South America literally farm fungi. They cut disks of leaves from plants and pile them up in gardens. Fungi are cultivated in these disk gardens, digesting the cellulose in the leaves that the ants cannot break down. Once smaller sugar molecules are produced and consumed by the fungi, the fungi in turn become a meal for the ants. The insects also patrol their garden, preying on competing fungi. Both ants and fungi benefit from the association. The fungus receives a steady supply of leaves and freedom from competition, while the ants feed on the fungi they cultivate.

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16.5F: Agrobacterium and Crown Gall Disease

Argobacterium causes Crown Gall Disease by transferring a DNA plasmid to the host plant, causing the host to make nutrients for it.

Learning Objectives

- Summarize the symbiotic relationship between plants and agrobacterium

Key Points

- Crown Gall Disease is caused by *Agrobacterium tumefacien*s, a bacteria that infects plants. The bacteria causes tumors on the stem of its host.
- *Agrobacterium tumefaciens* manipulates its hosts by transferring a DNA plasmid to the cells of its host. Plasmids are normally used to transfer DNA from bacteria to bacteria.
- Once in the host cell, the plasmid integrates itself into the host plant cell's genome and forces the host to produce unique amino acids and other substances which nourish the bacteria. These compounds are unusable by most bacteria, so Argobacteria can out-compete other species.

Key Terms

- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.
- **pilus**: A hair-like appendage found on the cell surface of many bacteria.

Crown Gall Disease is caused by a bacteria called *Agrobacterium tumefaciens*. The disease manifests as a tumor-like growth usually at the junction of the root and shoot. *A. tumefaciens* can transfer part of its DNA to the host plant, through a plasmid – a bacterial DNA molecule that is independent of a chromosome. The new DNA segment causes the plant to produce unusual amino acids and plant hormones which provide the bacteria with carbon and nitrogen.



Figure: **Smart plants cue farmers to nutrient deficiencies**: A. tumefaciens attaching itself to a plant cell

Bacteria normally use plasmids for horizontal gene transfer, so they can share genes with related bacteria to help them cope with stressful environments. For example, plasmids can confer on bacteria the ability to fix nitrogen, or to resist antibiotic compounds. Typically bacteria transfer plasmids through conjugation: a donor bacteria creates a tube called a pilus that penetrates the cell wall of the recipient bacteria and the plasmid DNA passes through the tube. The other bacteria either integrates the plasmid into its chromosomes, or it remains free-floating in the cytoplasm. In either case, the recipient bacteria receives new genetic material.

In the case of Crown Gall Disease, *A. tumefaciens* transfers a plasmid containing T-DNA into the cells of its host plant through conjugation, as it would with another bacteria. However, once inside the plant cell, the DNA integrates semi-randomly into the genome of the plant and changes the behavior of the celll.

The new plasmid genes are expressed by the plant cells, and cause them to secrete enzymes that produce the amino acids octopine or nopaline. It also carries genes for the biosynthesis of the plant hormones, auxin and cytokinins, and for the biosynthesis of opines, providing a carbon and nitrogen source for the bacteria.

These opines can be used by very few other bacteria and give *A. tumefaciens* a competitive advantage.

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16.5G: The Legume-Root Nodule Symbiosis

Legumes have a symbiotic relationship with bacteria called rhizobia, which create ammonia from atmospheric nitrogen and help the plant.

Learning Objectives

- Evaluate legume and nitrogen-fixing bacteria symbiosis

Key Points

- Rhizobia normally live in the soil, but when there is limited soil nitrogen, legumes release flavonoids which signal to rhizobia that the plant is seeking symbiotic bacteria.
- When exposed to flavonoids, the Rhizobia release *nodulation factor*, which stimulates the plant to create deformed root hairs. Rhizobia then form an ” infection thread” which allows them to enter the root cells through the root hairs.
- Once the rhizobia are inside the root cells, the root cells divide rapidly, forming a nodule.
- The rhizobia create ammonia from nitrogen in the air, which is used by the plant to create amino acids and nucleotides. The plant provides the bacteria with sugars.

Key Terms

- **Nodulation Factor**: Signaling molecules produced by bacteria known as rhizobia during the initiation of nodules on the root of legumes. A symbiosis is formed when legumes take up the bacteria.

Legumes and their Nitrogen-Fixing Bacteria

Many legumes have root nodules that provide a home for symbiotic nitrogen-fixing bacteria called *rhizobia*. This relationship is particularly common in nitrogen-limited conditions. The Rhizobia convert nitrogen gas from the atmosphere into ammonia, which is then used in the formation of amino acids and nucleotides.



Figure: **Root Nodules**: Root nodules are formed when nitrogen fixing bacteria called rhizobia enter the cells of a host plant.

Rhizobia normally live in the soil and can exist without a host plant. However, when legume plants encounter low nitrogen conditions and want to form a symbiotic relationship with rhizobia they release flavinoids into the soil. Rhizobia respond by releasing nodulation factor (sometimes just called *nod factor*), which stimulates nodule formation in plant roots. Exposure to nod factor triggers the formation of deformed root hairs, which permit rhizobia to enter the plant. Rhizobia then form an infection thread, which is an intercellular tube that penetrates the cells of the host plant, and the bacteria then enter the host plants cells through the deformed root hair. Rhizobia can also enter the root by inserting themselves between cracks between root cells; this method of infection is called *crack entry*. Bacteria enter the root cells from the intercellular spaces, also using an infection thread to penetrate cell walls. Infection triggers rapid cell division in the root cells, forming a nodule of tissue.

The relationship between a host legume and the rhizobia is symbiotic, providing benefits to both participants. Once the rhizobia have established themselves in the root nodule, the plant provides carbohydrates in the form of malate and succinate, and the rhizobia provide ammonia for the formation of amino acids. Many legumes are popular agricultural crops specifically because they require very little fertilizer: their rhiziobia fix nitrogen for them. Used properly some legumes can even serve as fertilizer for later crops, binding nitrogen in the plant remains in the soil.



Figure: **Soy Beans**: Soy beans are a type of legume crop that rely on rhizobia

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16.6: Microbial Bioremediation

Topic hierarchy

16.6A: Microbial Ore Leaching

16.6B: Petroleum Biodegradation

16.6C: The Degradation of Synthetic Chemicals in Soils and Water

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16.6A: Microbial Ore Leaching

Microbial ore leaching is the process in which microorganisms are used to extract metals from ores.

Learning Objectives

- Assess the advantages of microbial ore leaching

Key Points

- Bioleaching is cheaper than chemical extraction, safer for the environment, and more efficient in extracting metals with low concentration in ores.
- It is performed by iron and sulfide oxidizing bacteria or acid producing fungus.
- Bacteria recycle the major leaching reagent, like ferric iron, and perform further oxidation steps while gaining energy from the electron transfer.

Key Terms

- **ore leaching**: The process of recovering metals from ores by using a number of different techniques.

Microbial ore leaching (bioleaching) is the process of extracting metals from ores with the use of microorganisms. This method is used to recover many different precious metals like copper, lead, zinc, gold, silver, and nickel. Microorganisms are used because they can:

- lower the production costs.
- cause less environmental pollution in comparison to the traditional leaching methods.
- very efficiently extract metals when their concentration in the ore is low.

The Leaching Process

Bacteria perform the key reaction of regenerating the major ore oxidizer which in most cases is ferric iron as well as further ore oxidation. The reaction is performed at the bacterial cell membrane. In the process, free electrons are generated and used for the reduction of oxygen to water which produces energy in the bacterial cell.

Ores, like pyrite (FeS_2), are first oxidized by ferric iron (Fe^{3+}) to thiosulfate ($S_2O_3^{2-}$) in the absence of bacteria.

In the first step, disulfide is spontaneously oxidized to thiosulfate by ferric iron (Fe^{3+}), which in turn is reduced to give ferrous iron (Fe^{2+}):

(1) FeS2+6Fe3++3H2O⟶7Fe2++S2O2−3+6H+spontaneousFeS2+6Fe3++3H2O⟶7Fe2++S2O32−+6H+spontaneous

Bacteria are added in the second step and recover Fe^{3+} from ferrous iron (Fe^{2+}) which is then reused in the first step of leaching:

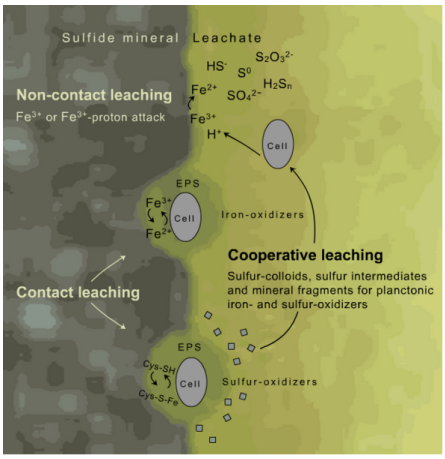

Figure: **Sulfide mineral bacterial leaching**: Bacterial cells oxidizing the ferrous iron back to ferric iron while using slightly different contact mechanisms with the metal.

(2) 4Fe2++O2+4H+⟶4Fe3++2H2O(iron oxidizers)4Fe2++O2+4H+⟶4Fe3++2H2O(iron oxidizers)

Thiosulfate is also oxidized by bacteria to give sulfate:

(3) $S2O2−3+2O2+H2O⟶2SO2−4+2H+$(sulfur oxidizers)$S2O32−+2O2+H2O⟶2SO42−+2H+$(sulfur oxidizers)

The ferric iron produced in reaction (2) oxidized more sulfide as in reaction (1), closing the cycle and given the net reaction:

(4) $2FeS2+7O2+2H2O⟶2Fe2++4SO2−4+4H+2FeS2+7O2+2H2O⟶2Fe2++4SO42−+4H+$

The net products of the reaction are soluble ferrous sulfate and sulfuric acid.

The microbial oxidation process occurs at the cell membrane of the bacteria. The electrons pass into the cells and are used in biochemical processes to produce energy for the bacteria while reducing oxygen to water. The critical reaction is the oxidation of sulfide by ferric iron. The main role of the bacterial step is the regeneration of this reactant.

Copper leaching has a very similar mechanism.

Microorganisms Capable of Ore Leaching

Bioleaching reactions industrially are performed by many bacterial species that can oxidize ferrous iron and sulfur. An example of such species is *Acidithiobacillus ferroxidans*. Some fungi species (*Aspergillus niger* and *Penicillium simplicissimum*) have also been shown to have the ability to dissolute heavy metals. When fungi are used, the leaching mechanism is different. The fungi use the acids that they produce in their metabolic reactions to dissolve the metal.

In general, bioleaching is cleaner and safer for the environment than chemical processing. However environmental pollution with toxic products, like sulfuric acid from the pyrite leaching, and heavy metals is still possible. Another drawback of microbial leaching is the slow rate at which microbes work.

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16.6B: Petroleum Biodegradation

Petroleum oil can be degraded by microorganisms that use it as a source of energy.

Learning Objectives

- Show how microbes biodegrade petroleum waste

Key Points

- Biodegradation is the process of breaking down material in simpler components by living organisms, most often microorganisms.
- Oil spills occur due to accidents in the industry as a result of extraction or transportation. Since such spills spread over great areas and have deleterious effects on living organisms. It is important to use environmentally friendly mechanisms for their cleanup.
- There are many microorganisms that can break down petroleum, the most prominent being hydrocarbonoclastic bacteria. A representative of this group is Alcanivorax borkumensis, and its genome contains genes that code for the degradation of alkanes.

Key Terms

- **hydrocarbons**: Organic compounds made only of carbon and hydrogen. Examples include alkanes, alkenes, and aromatic hydrocarbons.
- **emulsification**: The process of forming a mixture of substances that are nonmixable under normal conditions.
- **tarball**: A blob of petroleum oil.

Biodegradation is the process in which living organisms, most often microorganisms, break down material into simpler components. Such material is usually organic matter that could be dissolved into chemical elements by organisms that possess the metabolic pathways to perform the reactions. Some microorganisms produce enzymes that can degrade a variety of chemical compounds, including hydrocarbons like oil.

Petroleum (crude oil) is a liquid fossil fuel. It is a product of decaying organic matter, such as algae and zooplankton. It is one of the major energy sources in the world, and is also used by the chemical industry to manufacture a large number of consumer products. However, oil drilling or transportation can cause accidents that lead to contamination of the environment. Oil spills in marine environments are especially damaging because they cannot be contained and can spread over huge areas. The aromatic compounds in oil are toxic to living organisms and such spills can render havoc in an ecosystem. Natural seepages from unexplored oil sources is another source of contamination.

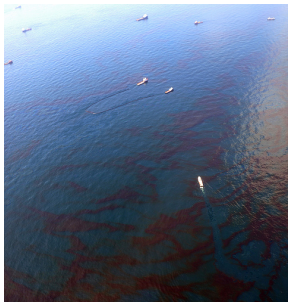

Figure: **The Deepwater Horizon Oil Spill**: This spill was the largest in the history of the oil industry and spread over huge areas.

In the environment, such spills are naturally cleaned by microorganisms that can break down the oil. The dominant group of such bacteria are the hydrocarbonoclastic bacteria (HCB). The concentration of these bacteria increases significantly in areas of oil spill. One of the best studied representative of this group is Alcanivorax borkumensis; it's also the only one to have its genome sequenced. This species contains individual genes responsible for breaking down certain alkanes into harmless products. It also possesses genes to direct the production of a layer of biosurfactant around the cell to enhance the oil emulsification. The addition of nitrogen and phosphorus to the Alcanivorax environment increases its growth rate. However, the addition of these nutrients in natural environments to improve the cleanup of oil spills is not desirable, since it can have an overall negative impact on the ecosystem.

Aside from hydrocarbons, crude oil contains additional toxic compounds, such as pyridine. These are degraded by representatives of other genera such as Micrococcus and Rhodococcus. Oil tarballs are biodegraded slowly by species from the genera Chromobacterium, Micrococcus, Bacillus, Pseudomonas, Candida, Saccharomyces and others. In the clean up of the Deepwater Horizon oil spill, genetically modified microorganisms were used, but some scientists suspect they might have caused health issues for people in the affected areas.

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16.6C: The Degradation of Synthetic Chemicals in Soils and Water

Microorganisms are crucial participants in the detoxification of water and soil.

Learning Objectives

- Distinguish bioremediation of soil vs. water

Key Points

- Bacteria decompose organic matter by producing a number of different enzymes for more general reactions such as hydrolysis, acetogenesis and methanogenesis, and highly specific enzymes such as deoxygenases that can break aromatic compounds.
- Bacterial species are assisted in the process of degradation by fungi (e.g., Aspergillus sp.), protozoa, and representatives of Archaea.
- The recent advances in genomics, proteomics, and bioinformatics fields allow new insights into the tremendous metabolic potential of microorganisms.

Key Terms

- **bioremediation**: The use of biological organisms, usually microorganisms, to remove contaminants, especially from polluted water.
- **bioavailability**: The amount of matter that is physicochemically accesible for degradation by microorganisms.

Our planet is contaminated with many chemicals that are toxic to living organisms. These chemicals are products or byproducts from different industries. Examples of such contaminants are polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), chloroethenes, and pharmaceutical substances. These pollutants can cause dangerous contamination of the air, soil, and water. Microorganisms play a major role in eliminating such pollutants from the environment.

Bioremediation of Soil

Soil is a major reservoir of microorganisms with each gram containing about one billion microbes. Microbes are used for bioremediation *in situ* of contaminated soil. Microorganisms that can remove contaminants from the environment are called bioremediators. Contaminations are most often caused by a mixture of pollutants and the best strategy for cleanup is to use a cocktail of different species since each one of them will be optimized for the degradation of a specific toxic compound.

The microbe activity is usually monitored on such sites to ensure optimal conditions for bacterial growth and hence degradation. Decomposition of the toxic substances can be performed both in the presence (aerobically) and absence (anaerobically) of oxygen. The limiting factor for bioremediaton in soils is the bioavailability of the contaminant agents.

Bioremediation of Water

The treatment of sewage water is a critical process to assure the purification of wastewater that will prevent chemical and microbiological pollution of the environment, especially for the drinking water supplies. An important part of this process is the biological step which involves the activity of living organisms to clean the water from organic matter. This happens in the secondary step of sewage purification. Microorganisms substantially lessen the concentration of nutrients which if released in the environment can lead to undesirable overgrowth of microorganisms and algae.



Figure: **Sewage Treatment Plant**: Wastewater treatment plants are critical in lowering the levels of pollutants in the environment.

They also have the potential to clean the water from toxic components. The degradation is performed in the anaerobic, aerobic, and composting steps. Anaerobic digestion by bacteria is allowed to procede for almost two weeks to guarantee enough time to

complete the process. During this time, the organic matter undergoes four different enzymatic transformations: *hydrolysis*, *acidogenesis*, *acetogenesis* and *methanogenesis*. The final products are water, carbon dioxide, and methane. In the aerobic step, oxygen is added into the system and the organic matter is converted to carbon dioxide. In the composting step, additional carbon sources are added to aid the final steps of degradation.

In recent years, advances in genomics, proteomics, and bioinformatics studies of environmental microorganisms have revealed a tremendous potential in metabolic pathways.

Such studies showed that *Burkholderia xenovorans* LB400 and *Rhodococcus* sp. strain RHA1, have evolved pathways to degrade aromatic compounds, which are some of the toughest contaminants to eliminate. The bacteria have genes coding for *deoxygenases* to open the aromatic ring structures of these chemicals.

Hydrocarbons and their derivatives were long believed to be degraded only in the presence of oxygen. This would often lead to oxygen depletion in environments heavily polluted with oil. Studies in recent years have proven that there are numerous anaerobic bacterial species capable of decomposing this group of pollutants. A common feature among these bacteria is that they possess *reductive dehalogenases*.

Bacterial species are assisted in the process of degradation by fungi (e.g., *Aspergillus* sp.), protozoa, and representatives of Archaea. The primary role of fungi is in secreting numerous extracellular enzymes that break down complex molecules into their components and make them readily available to the bacterial community.

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CHAPTER OVERVIEW

17: Industrial Microbiology

Industrial microbiology is a branch of biotechnology that applies microbial sciences to create industrial products in mass quantities. There are multiple ways to manipulate a microorganism to increase maximum product yields. Introduction of mutations into an organism many be accomplished by introducing them to mutagens. The medical application to industrial microbiology is the production of new drugs synthesized in a specific organism for medical purposes

17.1: Industrial Microbiology

17.1A: Industrial Microorganisms

17.1B: Molecular Products from Microbes

17.1C: Primary and Secondary Metabolites

17.1D: Large-Scale Fermentations

17.2: Microbial Products in the Health Industry

17.2A: Industrial Production of Antibiotics

17.2B: Vitamins and Amino Acids

17.2C: Steroids

17.2D: Enzymes Used in Industry

17.3: Wastewater Treatment and Water Purification

17.3A: Microorganisms and Water Quality

17.3B: Wastewater and Sewage Treatment

17.3C: Purification of Drinking Water

17.4: The Microbiology of Food

17.4A: Wine, Beer, and Alcohol

17.4B: Vinegar

17.4C: Citric Acid and Other Organic Compounds

17.4D: Edible Fungi

17.4E: Edible Algae

17.4F: Microbes and Dairy Products

17.5: Food Preservation

17.5A: Fermented Foods

17.5B: Food Spoilage by Microbes

17.5C: Food Preservation

Thumbnail: Märzen at Oktoberfest, served in the traditional 1-liter Maß.

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SECTION OVERVIEW

17.1: Industrial Microbiology

Topic hierarchy

17.1A: Industrial Microorganisms

17.1B: Molecular Products from Microbes

17.1C: Primary and Secondary Metabolites

17.1D: Large-Scale Fermentations

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17.1A: Industrial Microorganisms

There are various types of microorganisms that are used for large-scale production of industrial items.

Learning Objectives

- Describe how microorganisms are used in industry to manufacture food or products in large quantities

Key Points

- The ability of specific microorganisms to produce specialized enzymes and proteins has been exploited for many purposes in industry.
- Industrial microorganisms are used to produce many things, including food, cosmetics, pharmaceuticals and construction materials.
- Microorganisms can be genetically modified or engineered to aid in large-scale production.

Key Terms

- **exopolysaccharide**: a type of sugar-composed polymer secreted by a microorganism into the external environment
- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei that are fundamentally from bacteria.

Industrial microbiology includes the use of microorganisms to manufacture food or industrial products in large quantities. Numerous microorganisms are used within industrial microbiology; these include naturally occurring organisms, laboratory selected mutants, or even genetically modified organisms (GMOs). Currently, the debate in the use of genetically modified organisms (GMOs) in food sources is gaining both momentum, with more and more supporters on both sides. However, the use of microorganisms at an industrial level is deeply rooted into today's society. The following is a brief overview of the various microorganisms that have industrial uses, and of the roles they play.

Archaea are specific types of prokaryotic microbes that exhibit the ability to sustain populations in unusual and typically harsh environments. Those suriving in the most hostile and extreme settings are known as *extremophile archaea*. The isolation and identification of various types of *Archaea*, particularly the extremophile archaea, have allowed for analysis of their metabolic processes, which have then been manipulated and utilized for industrial purposes.

Extremophile archaea species are of particular interest due to the enzymes and molecules they produce that allow them to sustain life in extreme climates, including very high or low temperatures, extremely acid or base solutions, or when exposed to other harmful factors, including radiation. Specific enzymes which have been isolated and used for industrial purposes include thermostable DNA polymerases from the *Pyrococcus furiosus*. This type of polymerase isa common tool in molecular biology; it is capable of withstanding the high temperatures that are necessary to complete polymerase chain reactions. Additional enzymes isolated from *Pyrococcus* speciesinclude specific types of amylases and galactosidases which allow food processing to occur at high temperatrues as well.

Corynebacteria are characterized by their diverse origins. They are found in numerous ecological niches and are most often used in industry for the mass production of amino acids and nutritional factors. In particular, the amino acids produced by *Corynebacterium glutamicum* include the amino acid glutamic acid. Glutamic acid is used as a common additive in food production, where it is known as *monosodium glutamate* (MSG). *Corynebacterium* can also be used in steroid conversion and in the degradation of hydrocarbons. Steroid conversion is an important process in the development of pharmaceuticals. Degradation of hydrocarbons is key in the breakdown and elimination of environmental toxins. Items such as plastics and oils are hydrocarbons; the use of microorganisms which exhibit the ability to breakdown these compounds is critical for environmental protection.

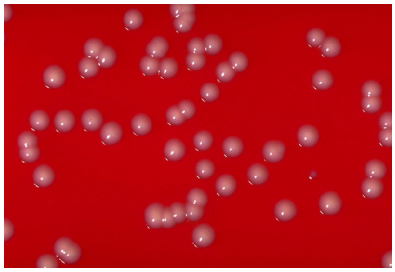

Figure: **Corynebacterium**: Corynebacterium species are often used to mass produce amino acids utilized in food processing.

Xanthomonas, a type of Proteobacteria, is known for its ability to cause disease in plants. The bacterial species which are classified under *Xanthomonas*exhibit the ability to produce the acidic exopolysaccharide commonly marketed as xanthan gum, used as a thickening and stabilizing agent in foods and in cosmetic ingredients to prevent separation.

Another type of microorganism utilized by industry includes various species of Aspergillus. Thisgenusincludes several hundred types of mold. *Aspergillus* has become a key component in industrial microbiology, where it is used in the production of alcoholic beverages and pharmaceutical development. *Aspergillus niger* is most commonly used to produce citric acid, which is used in numerous products ranging from household cleaners, pharmaceuticals, foods, cosmetics, photography and construction. Aspergillus is also commonly used in large-scale fermentation in the production of alcoholic beverages such as Japanese sake.

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17.1B: Molecular Products from Microbes

Learning Objectives

- Describe how Taq polymerase, restriction enzymes and DNA ligase are used in molecular biology

The expansion and growing popularity of the field of molecular biology has resulted in a higher demand for tools used to study molecular biology. The field of molecular biology specifically deals with the molecular mechanisms of a cell and focuses on the regulation of cellular interactions. Topics of particular interest within the field include gene expression (transcription and translation) and protein synthesis. Studying these mechanisms in the laboratory has been made possible by the use of molecules derived from microbes. The following is a brief overview of some of the molecular products derived from microbes that allow for the performance of popular molecular biology techniques.

Taq Polymerase

Taq polymerase is an enzyme that was first isolated from the microbe *Thermus aquaticus*. *T. aquaticus* is a specific type of bacterial species, a DNA polymerase, that is thermostable — it can withstand extremely high temperatures. The isolation of this polymerase has resulted in the ability to perform polymerase chain reactions (PCR), a process used to amplify DNA segments, in a single step. Prior to the isolation of Taq polymerase, a new DNA polymerase had to be added to the reaction after every cycle because of thermal denaturation. With the addition of Taq polymerase to the reaction tube, the cycle can be performed much more quickly, and less enzyme needs to be used. Currently, Taq polymerase is manufactured and produced on a large scale and is available for commercial sale.

Restriction Enzymes

Restriction enzymes are a specific class of enzymes isolated from various bacteria and archaea, in which they grow naturally as a means of protection against viral infection. These enzymes have the ability to cut DNA at specific recognition sequences and have served as invaluable tools in DNA modification and manipulation. The enzymes have the ability to recognize foreign DNA and cut it up. The bacteria and archaea from which these enzymes are isolated from have innate mechanisms to protect their own DNA sequences from these enzymes, such as methylation. The isolation of approximately 3000 restriction enzymes has allowed molecular biologists to utilize them in processes such as cloning and the production of recombinant DNA.

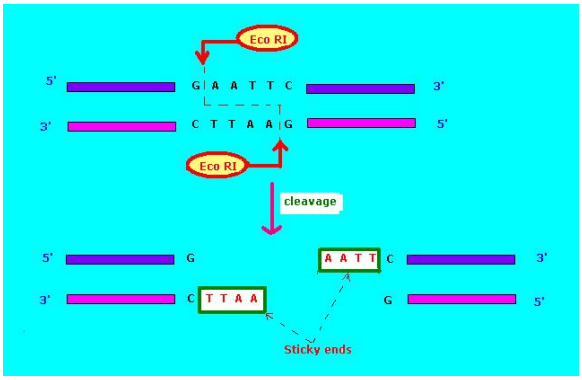

Figure: ***EcoRI Restriction Enzyme****: An example of a specific restriction enzyme, EcoRI, which exhibits the ability to target specific sequences within DNA.*

DNA Ligase

Another enzyme that was isolated from *T. aquaticus* and that has been undeniably important to the field of molecular biology is DNA ligase. DNA ligase plays a key role in molecular biology processes due to its ability to insert DNA fragments into plasmids. The process of DNA ligation is defined as the ability of DNA ligase to covalently link, or ligate, fragments of DNA together. In molecular biology — specifically, during the process of developing recombinant DNA — DNA ligase can be used to ligate a fragment of DNA into a plasmid vector. The most commonly used DNA ligase is derived from the T4 bacteriophage and is referred to as T4 DNA ligase.

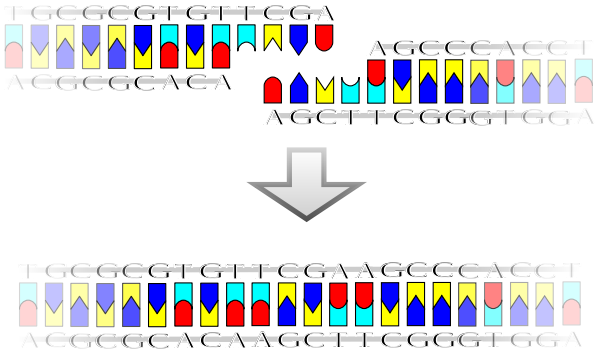

Figure: ***Example of a DNA Ligation****: Diagram of a DNA ligation.*

Key Points

- Various enzymes can be isolated from microorganisms and utilized in recombinant – DNA production.
- The ability of some archaea to thrive in extreme environments has led to analysis and isolation of important molecular components of the organisms, such as Taq polymerase, that have contributed to modern molecular biology techniques.
- Modern-day molecular biology techniques rely heavily on specific enzymes and molecular components derived from microbes, including DNA ligase and restriction enzymes.
- DNA ligase functions by covalently linking, or ligating, DNA fragments.
- Restriction enzymes function by recognizing and cutting specific sequences within DNA.

Key Terms

- **polymerase chain reaction**: A technique in molecular biology for creating multiple copies of DNA from a sample; used in genetic fingerprinting etc.
- **restriction enzymes**: an endonuclease that cuts DNA at specific recognition sequences

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17.1C: Primary and Secondary Metabolites

Primary and secondary metabolites are often used in industrial microbiology for the production of food, amino acids, and antibiotics.

Learning Objectives

- Describe how primary and secondary metabolites can be used in industrial microbiology to obtain amino acids, develop vaccines and antibiotics, and isolate chemicals for organic synthesis

Key Points

- Primary metabolites are considered essential to microorganisms for proper growth.
- Secondary metabolites do not play a role in growth, development, and reproduction, and are formed during the end or near the stationary phase of growth.
- These metabolites can be used in industrial microbiology to obtain amino acids, develop vaccines and antibiotics, and isolate chemicals necessary for organic synthesis.

Key Terms

- **bradycardia**: the slowing of the heartbeat to below average

Bacterial metabolism can be classified into three major categories: the kind of energy used for growth, the carbon source, and the electron donors used for growth. Pathogenic bacteria are capable of exhibiting various types of metabolism. Metabolites, the intermediates and products of metabolism, are typically characterized by small molecules with various functions. Metabolites can be categorized into both primary and secondary metabolites. These metabolites can be used in industrial microbiology to obtain amino acids, develop vaccines and antibiotics, and isolate chemicals necessary for organic synthesis.

Primary Metabolites

Primary metabolites are involved in growth, development, and reproduction of the organism. The primary metabolite is typically a key component in maintaining normal physiological processes; thus, it is often referred to as a central metabolite. Primary metabolites are typically formed during the growth phase as a result of energy metabolism, and are deemed essential for proper growth. Examples of primary metabolites include alcohols such as ethanol, lactic acid, and certain amino acids. Within the field of industrial microbiology, alcohol is one of the most common primary metabolites used for large-scale production. Specifically, alcohol is used for processes involving fermentation which produce products like beer and wine. Additionally, primary metabolites such as amino acids– including L-glutamate and L-lysine, which are commonly used as supplements– are isolated via the mass production of a specific bacterial species, *Corynebacteria glutamicum*. Another example of a primary metabolite commonly used in industrial microbiology includes citric acid. Citric acid, produced by *Aspergillus niger*, is one of the most widely used ingredients in food production. It is commonly used in pharmaceutical and cosmetic industries as well.

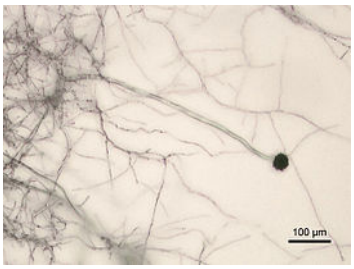

Figure: **Aspergillus niger**: Microorganisms such as Aspergillus niger are used in industrial microbiology for mass production of citric acid.

Secondary Metabolites

Secondary metabolites are typically organic compounds produced through the modification of primary metabolite synthases. Secondary metabolites do not play a role in growth, development, and reproduction like primary metabolites do, and are typically formed during the end or near the stationary phase of growth. Many of the identified secondary metabolites have a role in ecological function, including defense mechanism(s), by serving as antibiotics and by producing pigments. Examples of secondary

metabolites with importance in industrial microbiology include atropine and antibiotics such as erythromycin and bacitracin. Atropine, derived from various plants, is a secondary metabolite with important use in the clinic. Atropine is a competitive antagonist for acetycholine receptors, specifically those of the muscarinic type, which can be used in the treatment of bradycardia. Antibiotics such as erythromcyin and bacitracin are also considered to be secondary metabolites. Erythromycin, derived from *Saccharopolyspora erythraea*, is a commonly used antibiotic with a wide antimicrobial spectrum. It is mass produced and commonly administered orally. Lastly, another example of an antibiotic which is classified as a secondary metabolite is bacitracin. Bacitracin, derived from organisms classified under *Bacillus subtilis*, is an antibiotic commonly used a topical drug. Bacitracin is synthesized in nature as a nonribosomal peptide synthetase that can synthesize peptides; however, it is used in the clinic as an antibiotic.



Figure: **Erythromycin tablets**: Erythromycin is an example of a secondary metabolite used as an antibiotic and mass produced within industrial microbiology.

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17.1D: Large-Scale Fermentations

Large-scale fermentations are key to the production of numerous products ranging from food to pharmaceutical items.

Learning Objectives

- Describe fermentation and its applications to produce food, alcoholic beverages, fuel and recombinant products such as insulin

Key Points

- Large-scale fermentations are utilized to create massive quantities of ethanol which are used for food production, alcohol production, and even gasoline production.
- Fermentation is characterized by the metabolic processes that are used to transfer electrons released from nutrients to molecules obtained from the breakdown of those same nutrients.
- Fermentation utilizes numerous organic compounds, such as sugars, as endogenous electron acceptors to promote the electron transfer that occurs.

Key Terms

- **oxidation**: A reaction in which the atoms of an element lose electrons and the valence of the element increases.
- **amylase**: A type of digestive enzyme capable of breaking down complex carbohydrates into simple sugars.

Fermentation includes the processes by which energy is extracted from the oxidation of organic compounds. The oxidation of organic compounds occurs by utilizing an endogenous electron acceptor to transfer electrons released from nutrients to molecules obtained from the breakdown of these same nutrients.

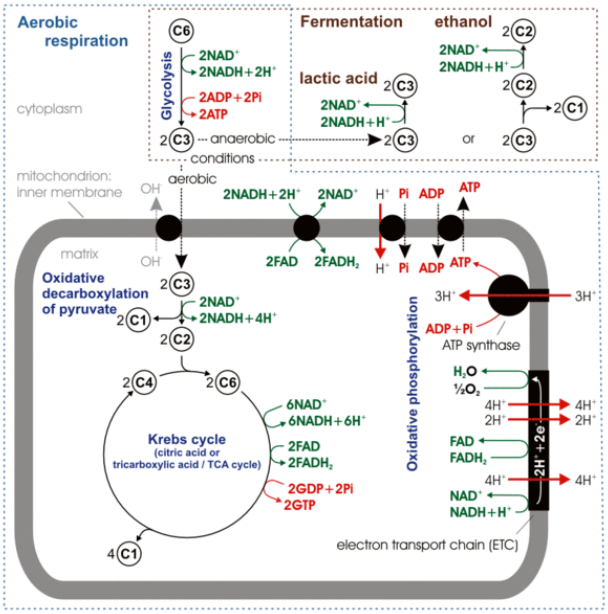

Figure: **Common types of fermentation**: These are common types of fermentation utilized in eukaryotic cells.

There are various types of fermentation which occur at the industrial level such as ethanol fermentation and fermentation processes used to produce food and wine. The ability to utilize the fermentation process in anaerobic conditions is critical to organisms which demand ATP production by glycolysis. Fermentation can be carried out in aerobic conditions as well, as in the case of yeast cells which prefer fermentation to oxidative phosphorylation. The following is a brief overview of a few types of the large-scale fermentations utilized by industries in production creation.

Ethanol Fermentation

Ethanol fermentation is used to produce ethanol for use in food, alcoholic beverages, and both fuel and industry. The process of ethanol fermentation occurs when sugars are converted into cellular energy. The sugars which are most often used include glucose,

fructose, and sucrose. These sugars are converted into cellular energy and produce both ethanol and carbon dioxide as waste products. Yeast is the most commonly used organism to produce ethanol via the fermentation process for beer, wine, and alcoholic drink production. As stated previously, despite abundant amounts of oxygen which may be present, yeast prefer to utilize fermentation. Hence, the use of yeast on a large-scale to produce ethanol and carbon dioxide occurs in an anaerobic environment.

The ethanol which is produced can then be used in bread production. Yeast will convert the sugars present in the dough to cellular energy and produce both ethanol and carbon dioxide in the process. The ethanol will evaporate and the carbon dioxide will expand the dough. In regards to alcohol production, yeast will induce fermentation and produce ethanol. Specifically, in wine-making, the yeast will convert the sugars present in the grapes. In beer and additional alcohol such as vodka or whiskey, the yeast will convert the sugars produced as a result of the conversion of grain starches to sugar by amylase. Additionally, yeast fermentation is utilized to mass produce ethanol which is added to gasoline. The major source of sugar utilized for ethanol production in the US is currently corn; however, crops such as sugarcane or sugar beets can be used as well.



Figure: **Fermentation in grapes**: This is a photograph of grapes undergoing fermentation during the wine-making process.

Recombinant Products

Fermentation is also utilized in the mass production of various recombinant products. These recombinant products include numerous pharmaceuticals such as insulin and hepatitis B vaccine. Insulin, produced by the pancreas, serves as a central regulator of carbohydrate and fat metabolism and is responsible for the regulation of glucose levels in the blood. Insulin is used medically to treat individuals diagnosed with diabetes mellitus. Specifically, individuals with type 1 diabetes are unable to produce insulin and those with type 2 diabetes often develop insulin resistance where the hormone is no longer effective.

The increase in individuals diagnosed with diabetes mellitus has resulted in an increase in demand for external insulin. The mass production of insulin is performed by utilizing both recombinant DNA technology and fermentation processes. *E. coli*, which has been genetically altered to produce proinsulin, is grown to a large amount to produce sufficient amounts in a fermentation broth. The proinsulin is then isolated via disruption of the cell and purified. There is further enzymatic reactions that occur to then convert the proinsulin to crude insulin which can be further altered for use as a medicinal compound.

An additional recombinant product that utilizes the fermentation process to be produced is the hepatitis B vaccine. The hepatitis B vaccine is developed to specifically target the hepatitis B virus infection. The creation of this vaccine utilizes both recombinant DNA technology and fermentation. A gene, HBV, which is specific for hepatitis B virus, is inserted into the genome of the organism yeast. The yeast is used to grow the HBV gene in large amounts and then harvested and purified. The process of fermentation is utilized to grow the yeast, thus promoting the production of large amounts of the HBV protein which was genetically added to the genome.

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SECTION OVERVIEW

17.2: Microbial Products in the Health Industry

Topic hierarchy

17.2A: Industrial Production of Antibiotics

17.2B: Vitamins and Amino Acids

17.2C: Steroids

17.2D: Enzymes Used in Industry

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17.2A: Industrial Production of Antibiotics

Industrially produced antibiotics are produced by fermentation, where the source microorganism is grown in large liquid growth medium.

Learning Objectives

- Describe how antibiotics are produced in industry by fermentation

Key Points

- Antibiotics are the secondary metabolites of microorganisms.
- During processing, the antibiotic must be extracted and purified to a crystalline product.
- Useful antibiotics are often discovered using a screening process or a rational design process.

Key Terms

- **antibiotic**: Any substance that can destroy or inhibit the growth of bacteria and similar microorganisms.
- **fermentation**: Any of many anaerobic biochemical reactions in which an enzyme (or several enzymes produced by a microorganism) catalyses the conversion of one substance into another; especially the conversion (using yeast) of sugars to alcohol or acetic acid with the evolution of carbon dioxide.
- **metabolite**: Any substance produced by, or taking part in, a metabolic reaction.

Antibiotics are produced industrially by a process of fermentation, where the source microorganism is grown in large containers (100,000 – 150,000 liters or more) containing a liquid growth medium.

Oxygen concentration, temperature, pH, and nutrient levels must be optimal and are closely monitored and adjusted if necessary. As antibiotics are secondary metabolites, the population size must be controlled very carefully to ensure that maximum yield is obtained before the cells die. Once the process is complete, the antibiotic must be extracted and purified to a crystalline product. This is simpler to achieve if the antibiotic is soluble in organic solvent. Otherwise it must first be removed by ion exchange, adsorption, or chemical precipitation.

Microorganisms used in fermentation are rarely identical to their counterparts in the wild. This is because species are often genetically modified to yield the maximum amounts of antibiotics. Mutation is often used and is encouraged by introducing mutagens such as ultraviolet radiation, x-rays, or certain chemicals. Selection and further reproduction of the higher yielding strains over many generations can raise yields by 20-fold or more. Another technique used to increase yields is gene amplification, where copies of genes coding for enzymes involved in the antibiotic production can be inserted back into a cell, via vectors such as plasmids. This process must be closely linked with retesting of antibiotic production and effectiveness.



Figure: **An agar plate with microorganisms**: This is an agar plate streaked with microorganisms.

Despite the wide variety of known antibiotics, less than 1% of antimicrobial agents have medical or commercial value. For example, whereas penicillin has a high therapeutic index as it does not generally affect human cells, this is not the case for many antibiotics. Other antibiotics simply lack advantage over those already in use or have no other practical applications.

Useful antibiotics are often discovered using a screening process. To conduct such a screen, isolates of many different microorganisms are cultured and then tested for production of diffusible products that inhibit the growth of test organisms. Most antibiotics identified in such a screen are already known and must therefore be disregarded. The remainder must be tested for their selective toxicities and therapeutic activities, and the best candidates can be examined and possibly modified.

A more modern version of this approach is a rational design program. This involves screening directed towards finding new natural products that inhibit a specific target, such as an enzyme only found in the target pathogen, rather than tests to show general

inhibition of a culture.

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17.2B: Vitamins and Amino Acids

Microorganisms and plants can synthesize many uncommon amino acids and vitamins.

Learning Objectives

- Describe how microorganisms and plants can synthesize many uncommon amino acids and vitamins

Key Points

- Amino acids are organic compounds made from amine (-NH2) and carboxylic acid (-COOH) functional groups, and a specific side-chain.
- Vitamin K is a group of structurally similar, fat-soluble vitamins that are needed for the posttranslational modification of certain proteins.
- Bacteria in the colon (large intestine) can produce a range of vitamin K2 forms, and can also convert vitamin K1 into vitamin K2.

Key Terms

- **amino acid**: Any organic compound containing both an amino and a carboxylic acid functional group.
- **vitamin**: Any of a specific group of organic compounds essential in small quantities for healthy human growth, metabolism, development, and body function; found in minute amounts in plant and animal foods or sometimes produced synthetically; deficiencies of specific vitamins produce specific disorders.
- **synthesize**: To combine two or more things to produce a new, more complex product.
- **dichotomous key**: a tool for identification of plants and animals, written as a sequence of paired questions, the choice of which determines the next pair of questions until a name or identification is reached

Amino Acids

Amino acids are biologically important organic compounds made from amine (-NH2) and carboxylic acid (-COOH) functional groups, along with a side-chain specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen. About 500 amino acids are known which can be classified in many ways.

Microorganisms and plants can synthesize many uncommon amino acids. For example, some microbes make 2-aminoisobutyric acid and lanthionine, which is a sulfide-bridged derivative of alanine. Both of these amino acids are found in peptidic lantibiotics such as alamethicin. While in plants, 1-aminocyclopropane-1-carboxylic acid is a small disubstituted cyclic amino acid that is a key intermediate in the production of the plant hormone ethylene.

Vitamins

Vitamin K is a group of structurally similar, fat-soluble vitamins that are needed for the posttranslational modification of certain proteins required for blood coagulation and in metabolic pathways in bone and other tissue. They are 2-methyl-1,4-naphthoquinone (3-) derivatives. This group of vitamins includes two natural vitamers: vitamin K1 and vitamin K2.

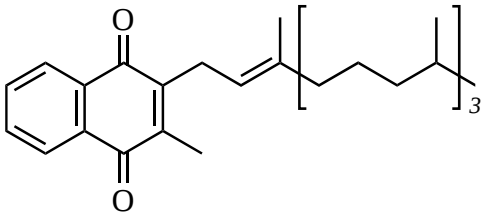

Figure: **Vitamin K1 (phylloquinone)**: This is vitamin K1 (phylloquinone). Both forms of the vitamin contain a functional naphthoquinone ring and an aliphatic side-chain. Phylloquinone has a phytyl side-chain.

Vitamin K1, also known as phylloquinone or phytomenadione (also called phytonadione), is synthesized by plants, and is found in highest amounts in green leafy vegetables because it is directly involved in photosynthesis.

Vitamin K2 has several subtypes, one of which is involved in bone metabolism. Vitamin K2 homologs (menaquinones) are characterized by the number of isoprenoid residues in their side chain. Menaquinones are abbreviated MK-n, where n represents the

number of isoprenoid side chain residues. For example, menaquinone-4 (abbreviated MK-4), has four isoprene residues in its side chain. Bacteria in the colon (large intestine) can produce a range of vitamin K2 forms, and can also convert K1 into K2 (MK-7 homolog). No known toxicity exists for vitamins K1 or K2.

Three synthetic types of vitamin K are known: vitamins K3, K4, and K5. Although the natural K1 and K2 forms are nontoxic, the synthetic form K3 (menadione) has shown toxicity.

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17.2C: Steroids

Learning Objectives

- Describe steroid biosynthesis

A steroid is a type of organic compound that contains a characteristic arrangement of four cycloalkane rings that are joined to each other. Examples of steroids include the dietary fat cholesterol, the sex hormones estradiol and testosterone, and the anti-inflammatory drug dexamethasone. The core of steroids is composed of twenty carbon atoms bonded together that take the form of four fused rings: three cyclohexane rings (designated as rings A, B, and C in the figure to the right) and one cyclopentane ring (the D ring). The steroids vary by the functional groups attached to this four-ring core and by the oxidation state of the rings. Sterols are special forms of steroids, with a hydroxyl group at position-3 and a skeleton derived from cholestane.

Hundreds of distinct steroids are found in plants, animals, and fungi. All steroids are made in cells either from the cycloartenol (plants) or sterols lanosterol (animals and fungi). Both lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.

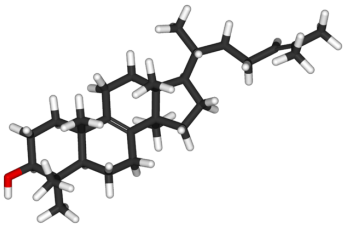

Figure: **Steroid Lanosterol**: This is the stick model of the steroid lanosterol. The total number of carbons (30) reflects its triterpenoid origin.

Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals compared to many other organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In humans and other animals, the biosynthesis of steroids follows the mevalonate pathway that uses acetyl-CoA as building blocks to form dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). In plants and bacteria, the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates.

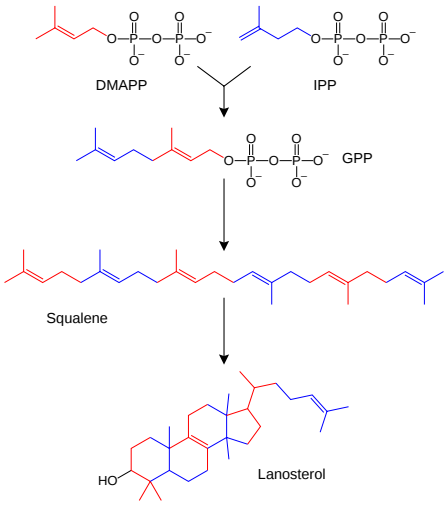

Figure: **Steroid Synthesis**: This is a simplified version of the latter part of steroid synthesis pathway, where the intermediates isopentenyl pyrophosphate (PP or IPP) and dimethylallyl pyrophosphate (DMAPP) form geranyl pyrophosphate (GPP), squalene and, finally, lanosterol, the first steroid in the pathways. Some intermediates are omitted for clarity.

The non-mevalonate pathway or 2-C-methyl-D-erythritol 4-phosphate/1-deoxy-D-xylulose 5-phosphate pathway (MEP/DOXP pathway) of isoprenoid biosynthesis is an alternative metabolic pathway leading to the formation of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP).

The classical mevalonate pathway or HMG-CoA reductase pathway is an important cellular metabolic pathway present in all higher eukaryotes and many bacteria. It is important for the production of IPP and DMAPP that serve as the basis for the biosynthesis of molecules used in processes as diverse as protein prenylation, cell membrane maintenance, hormones, protein anchoring, and N-glycosylation.

In contrast to the classical mevalonate pathway of isoprenoid biosynthesis, plants and apicomplexan protozoa such as malaria parasites have the ability to produce their isoprenoids (terpenoids) using an alternative pathway, the non-mevalonate pathway, which takes place in their plastids. In addition, most bacteria including important pathogens such as Mycobacterium tuberculosis synthesize IPP and DMAPP via the non-mevalonate pathway.

Key Points

- Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors.
- In plants and bacteria, the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates.
- The classical mevalonate pathway or HMG-CoA reductase pathway is an important cellular metabolic pathway present in all higher eukaryotes and many bacteria.

Key Terms

- **steroid**: A class of organic compounds having a structure of 17 carbon atoms arranged in four rings; they are lipids, and occur naturally as sterols, bile acids, adrenal and sex hormones, and some vitamins; many drugs are synthetic steroids.
- **anabolic**: Anabolism is the set of metabolic pathways that construct molecules from smaller units.
- **biosynthesis**: The synthesis of organic compounds within a living organism, especially the synthesis of large compounds from small ones.

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17.2D: Enzymes Used in Industry

Enzymes are biological molecules that catalyze (increase the rates of) chemical reactions.

Learning Objectives

- Describe the use of enzymes in industry

Key Points

- Since enzymes are selective for their substrates and speed up only a few reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell.
- Synthetic molecules called artificial enzymes also display enzyme-like catalysis.
- Enzymes are used in the chemical industry and other industrial applications when extremely specific catalysts are required.

Key Terms

- **chemical reactions**: Processes that lead to the transformation of one set of chemical substances to another.
- **rennin**: a proteolytic enzyme, obtained the gastric juice of the abomasum of calves, used to coagulate milk and make cheese
- **enzymes**: Biological molecules that catalyze (i.e., increase the rates of) chemical reactions.
- **Synthetic**: The combination of two or more parts, whether by design or by natural processes. It may imply being prepared or made artificially, in contrast to naturally.

Enzymes are biological molecules that catalyze (increase the rates of) chemical reactions. In enzymatic reactions, the molecules at the beginning of the process, called substrates, are converted into different molecules, called products. Almost all chemical reactions in a biological cell need enzymes in order to occur at rates sufficient for life. Since enzymes are selective for their substrates and speed up only a few reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell.

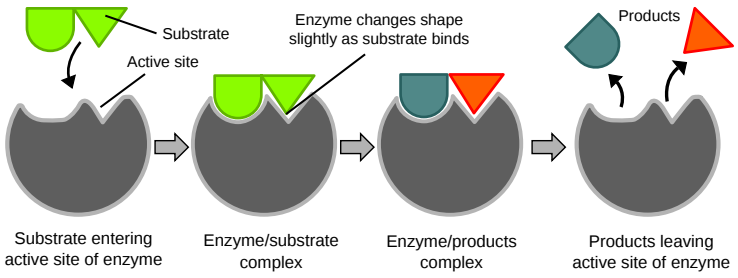

Figure: **Enzymatic Catalysis**: Model of enzymatic catalysis

Like all catalysts, enzymes work by lowering the activation energy for a reaction, thus dramatically increasing the rate of the reaction. As a result, products are formed faster and reactions reach their equilibrium state more rapidly. Most enzyme reaction rates are millions of times faster than those of comparable un-catalyzed reactions.

As with all catalysts, enzymes are not consumed by the reactions they catalyze, nor do they alter the equilibrium of these reactions. However, enzymes do differ from most other catalysts in that they are highly specific for their substrates. A few RNA molecules called ribozymes also catalyze reactions, with an important example being some parts of the ribosome. Synthetic molecules, called artificial enzymes, also display enzyme-like catalysis.

Enzyme activity can be affected by other molecules. Inhibitors can decrease enzyme activity; activators can increase activity. Many drugs and poisons are enzyme inhibitors. Activity is also affected by temperature, pressure, chemical environment (e.g., pH), and substrate concentration. Some enzymes are used commercially; for example, in the synthesis of antibiotics. In addition, some household products use enzymes to speed up biochemical reactions (e.g., enzymes in biological washing powders break down protein or fat stains on clothes; enzymes in meat tenderizers break down proteins into smaller molecules, making the meat easier to chew).

Enzymes are used in the chemical industry and other industrial applications when extremely specific catalysts are required. However, enzymes in general are limited in the number of reactions they have evolved to catalyze, and by their lack of stability in organic solvents and at high temperatures. As a consequence, protein engineering is an active area of research and involves

attempts to create new enzymes with novel properties, either through rational design or in vitro evolution. These efforts have begun to be successful, and a few enzymes have now been designed “from scratch” to catalyze reactions that do not occur in nature.

In food processing, the enzymes used include amylases from fungi and plants. These enzymes are used in the production of sugars from starch, such as in making high-fructose corn syrup. In baking, they catalyze the breakdown of starch in the flour to sugar. Yeast fermentation of sugar produces the carbon dioxide that raises the dough. Proteases are used by biscuit manufacturers to lower the protein level of flour. Trypsin is used to predigest baby foods. For the processing of fruit juices, cellulases and pectinases are used to clarify fruit juices. Papain is used to tenderize meat for cooking.

In the dairy industry, rennin, derived from the stomachs of young ruminant animals (like calves and lambs) is used to manufacture of cheese, used to hydrolyze protein. Lipases are implemented during the production of Roquefort cheese to enhance the ripening of the blue-mold cheese. Lactases are used to break down lactose to glucose and galactose.

In the brewing industry, enzymes from barley are released during the mashing stage of beer production. They degrade starch and proteins to produce simple sugar, amino acids, and peptides that are used by yeast for fermentation. Industrially-produced barley enzymes are widely used in the brewing process to substitute for the natural enzymes found in barley. Amylase, glucanases, and proteases are used to split polysaccharides and proteins in the malt. Betaglucanases and arabinoxylanases are used to improve the wort and beer filtration characteristics. Amyloglucosidase and pullulanases are used for low-calorie beer and adjustment of fermentability. Proteases are used to remove cloudiness produced during storage of beers.

In the starch industry, amylases, amyloglucosideases, and glucoamylases convert starch into glucose and various syrups. Glucose isomerase converts glucose into fructose in production of high-fructose syrups from starchy materials.

In the paper industry, amylases, xylanases, cellulases, and ligninases are used to degrade starch to lower viscosity, aiding sizing and coating paper.

In the biofuel industry, cellulases used to break down cellulose into sugars that can be fermented (see cellulosic ethanol).

In the production of biological detergents, proteases, produced in an extracellular form from bacteria, are used in pre-soak conditions and direct liquid applications, helping with the removal of protein stains from clothes.

In molecular biology, restriction enzymes, DNA ligase, and polymerases are used to manipulate DNA in genetic engineering, important in pharmacology, agriculture and medicine, and are essential for restriction digestion and the polymerase chain reaction. Molecular biology is also important in forensic science.

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SECTION OVERVIEW

17.3: Wastewater Treatment and Water Purification

Topic hierarchy

17.3A: Microorganisms and Water Quality

17.3B: Wastewater and Sewage Treatment

17.3C: Purification of Drinking Water

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17.3A: Microorganisms and Water Quality

Microorganisms from sewage can cause human disease, but can also negatively affect important ecosystems on which humans rely.

Learning Objectives

- Explain the relationship between microorganisms and water quality

Key Points

- Scientists typically measure water quality by testing for the presence of "indicator species " of bacteria, harmless microorganisms that are found in the human gut alongside pathogenic species.
- Typical indicator species include coliform bacteria (related to the pathogenic E. coli) and Pseudomonas aeruginosa. When levels of these bacteria are high, scientists begin testing for disease causing bacteria.
- Ecosystems may also suffer from contaminated water. In aquatic ecosystems, sewage bacteria may cause "dead zones" when they use up the oxygen in the water while decomposing nutrients. Coral reefs may also become infected with sewage bacteria and die.

Key Terms

- **hypoxic**: Of, pertaining to, or suffering from hypoxia (lack of oxygen)

Water Quality and Human Health

Waterborne diseases are a infections transmitted by contaminated drinking water. Although there are many pathogens which can be transmitted through water, bacteria and protozoa are some of the most common organisms that cause disease. Monitoring for waterborne disease can be difficult because humans often shed very low numbers of pathogenic bacteria when they are infected. To test whether disease causing bacteria might be present, researchers measure the presence of indicator species, such as coliform bacteria (which are the group to which the pathogenic *E. coli* belongs) or*Pseudomonas aeruginosa*. Although most coliform bacteria do not cause disease, they are commonly found in the human gut and in sewage, and their presence implies that human waste has reached the water supply. Researchers usually test water quality by sampling water and measuring the concentration of all bacteria in a sample. If the number of bacteria exceeds the limits set by water quality standards, the next step is to test for the presence of specific pathogens. Scientists can use genetic probes, or specific culture techniques to check whether harmful pathogens are present. Standards for testing may differ depending on the water source: drinking water is held to very high standards, while water quality in lakes and rivers may be held to more lax standards because recreational swimmers typically ingest very little water.

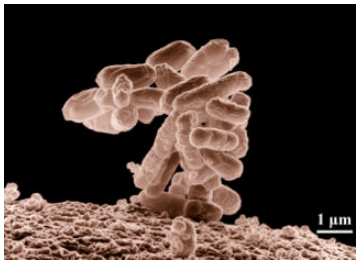

Figure: **E. coli Bacteria**: Researchers monitor water quality by testing for coliform bacteria, relatives of E. coli

Water Quality and The Environment

Microrganisms can also have important impacts on the environment. All healthy ecosystems have their own communities of bacteria that decompose biological matter. However, contamination by sewage and human waste can disrupt the natural balance of bacteria and affect aquatic ecosystems. An influx of human pathogens can cause problems for ecosystems in several ways. First, sewage bacteria can cause hypoxic "dead zones" in aquatic ecosystems. The foreign bacteria rapidly reproduce and consume debris and nutrients in the sewage, but use up all the oxygen in the water in doing so. The de-oxygenated water is harmful to fish and other aquatic life. Coral reefs are also affected by sewage contaminated water. Coral can become infected by human gut bacteria, and this can cause "coral bleaching disease" where coral lose their normal bacterial and algae communities and die. Water quality is not just important for human health, it is important for the human communities that depend on aquatic and marine ecosystems.

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17.3B: Wastewater and Sewage Treatment

Wastewater is treated in 3 phases: primary (solid removal), secondary (bacterial decomposition), and tertiary (extra filtration).

Learning Objectives

- List the steps of wastewater/sewage treatment

Key Points

- Primary treatment is the first phase of sewage treatment: wastewater is placed in a holding tank and solids settle to the bottom where they are collected and lighter substances like fats and oils are scraped off the top.
- Secondary treatment is where waste is broken down by aerobic bacteria incorporated into the wastewater treatment system.
- Tertiary treatment is designed to filter out nutrients and waste particles that might damage sensitive ecosystems; wastewater is passed through additional filtering lagoons or tanks to remove extra nutrients.

Key Terms

- **Effluent**: Sewage water that has been partially treated and is released into a natural body of water; a flow of any liquid waste.
- **zooplankton**: Small protozoa, crustaceans (such as krill), and the eggs and larvae from larger animals.
- **aerobic**: Living or occurring only in the presence of oxygen.

Sewage is generated by residential and industrial establishments. It includes household waste liquid from toilets, baths, showers, kitchens, sinks, and so forth that is disposed of via sewers. In many areas, sewage also includes liquid waste from industry and commerce. The separation and draining of household waste into greywater and blackwater is becoming more common in the developed world. Greywater is water generated from domestic activities such as laundry, dishwashing, and bathing, and can be reused more readily. Blackwater comes from toilets and contains human waste.

Sewage treatment is done in three stages: primary, secondary and tertiary treatment.

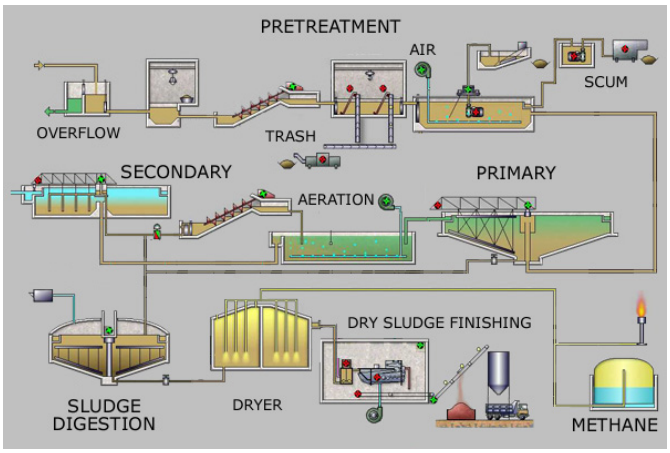

Figure: **Diagram of Sewage Treatment Process**: Sewage passes through primary, secondary, and tertiary treatment.

Primary Treatment

In primary treatment, sewage is stored in a basin where solids (sludge) can settle to the bottom and oil and lighter substances can rise to the top. These layers are then removed and then the remaining liquid can be sent to secondary treatment. Sewage sludge is treated in a separate process called sludge digestion.

Secondary Treatment

Secondary treatment removes dissolved and suspended biological matter, often using microorganisms in a controlled environment. Most secondary treatment systems use aerobic bacteria, which consume the organic components of the sewage (sugar, fat, and so on). Some systems use fixed film systems, where the bacteria grow on filters, and the water passes through them. Suspended growth systems use “activated” sludge, where decomposing bacteria are mixed directly into the sewage. Because oxygen is critical to bacterial growth, the sewage is often mixed with air to facilitate decomposition.

Tertiary Treatment

Tertiary treatment (sometimes called “effluent polishing”) is used to further clean water when it is being discharged into a sensitive ecosystem. Several methods can be used to further disinfect sewage beyond primary and secondary treatment. Sand filtration, where water is passed through a sand filter, can be used to remove particulate matter. Wastewater may still have high levels of nutrients such as nitrogen and phosphorus. These can disrupt the nutrient balance of aquatic ecosystems and cause algae blooms and excessive weed growth. Phosphorus can be removed biologically in a process called enhanced biological phosphorus removal. In this process, specific bacteria, called polyphosphate accumulate organisms that store phosphate in their tissue. When the biomass accumulated in these bacteria is separated from the treated water, these biosolids have a high fertilizer value. Nitrogen can also be removed using nitrifying bacteria. Lagooning is another method for removing nutrients and waste from sewage. Water is stored in a lagoon and native plants, bacteria, algae, and small zooplankton filter nutrients and small particles from the water.

Sludge Digestion

Sewage sludge scraped off the bottom of the settling tank during primary treatment is treated separately from wastewater. Sludge can be disposed of in several ways. First, it can be digested using bacteria; bacterial digestion can sometimes produce methane biogas, which can be used to generate electricity. Sludge can also be incinerated, or condensed, heated to disinfect it, and reused as fertilizer.

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17.3C: Purification of Drinking Water

Water is purified with filters to remove larger protozoans, and by chemical or UV disinfection to kill bacteria and other small pathogens.

Learning Objectives

- Illustrate the steps of drinking water purification

Key Points

- Water is first passed through a system of filters and a coagulating agent is added to remove particulate matter.
- Water is then passed through a membrane filter to remove large pathogens such as cryptosporidum and giardia.
- To finalize the purification process, chemical disinfection (usually with chlorine or ozone) or UV light is applied to the water to kill bacteria, viruses, and the hardy cysts produced by cryptosporidium and giardia.

Key Terms

- **ozone**: A triatomic molecule, consisting of three oxygen atoms. It is an allotrope of oxygen that is much less stable than the diatomic allotrope (O2), breaking down with a half life of about half an hour in the lower atmosphere, to normal dioxygen. Ozone is formed from dioxygen by the action of ultraviolet light and also atmospheric electrical discharges, and is present in low concentrations throughout the Earth's atmosphere. In total, ozone makes up only 0.6 parts per million of the atmosphere.
- **coagulation**: The precipitation of suspended particles as they increase in size (by any of several physical or chemical processes).
- **protozoa**: Protozoa are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior, e.g., movement. Protozoa were regarded as the partner group of protists to protophyta, which have plant-like behaviour, e.g., photosynthesis.

Drinking Water Purification

In order to purify drinking water from a source (such as a lake, river, reservoir or groundwater), the water must go through several steps to remove large particles and different types of pathogens.



Figure: **Drinking Water Purification**: Water is purified for drinking through a system of filters and by chemical disinfectant.

1. Pumping and Containment: Water is pumped from the source into holding tanks.
2. Screening: Water is passed through a screen filter to remove large debris.
3. Storage: Water is stored in reservoirs, tanks, and water towers in preparation for purification. Sometimes water is "pre-cholrinated" in this system to prevent bacterial growth while it is in storage.
4. Coagulation and Sedimentation: Although there are many processes by which large particles are removed from drinking water, most water purification systems implement some kind of coagulation system. A chemical that causes particle aggregation is added to the water, and clumps of particles form and settle to the bottom of the reservoir. This is called sedimentation.
5. Membrane Filtration: Membrane filters are able to remove all particles larger than 0.2 um. Larger pathogens such as giardia lamblia and cryptosporidium are trapped in these filters, but the cysts they produce are small enough to pass through.
6. Disinfection: Before water is considered potable, it must be disinfected to remove any pathogens that passed through the membrane filter.

Methods of Disinfection

- Chlorination is the most common form of disinfection. Chlorine is a strong oxidant, and rapidly kills many microorganisms, especially bacteria. Because chlorine is a toxic gas, it can also be dangerous to sanitation workers. Chlorine based compounds like choloramine are often used. Although chlorine is very effective against bacteria, it is not as effective against the cysts formed by protozoans (like giardia lamblia and cryptosporidium). Chlorine can sometimes leave residual byproducts in water.
- Ozone is an unstable molecule that readily gives up one atom of oxygen providing a powerful oxidizing agent. This agent is toxic to most waterborne organisms. Ozone is widely used in Europe, and is an effective method to kill cysts formed by protozoans. It also works well against almost all other pathogens.
- Ultraviolet Light is very effective at inactivating protozoan cysts, and will also kill bacteria and viruses. However, it is not as effective in cloudy water. It is sometimes used in concert with chlorination.

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SECTION OVERVIEW

17.4: The Microbiology of Food

Topic hierarchy

17.4A: Wine, Beer, and Alcohol

17.4B: Vinegar

17.4C: Citric Acid and Other Organic Compounds

17.4D: Edible Fungi

17.4E: Edible Algae

17.4F: Microbes and Dairy Products

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17.4A: Wine, Beer, and Alcohol

The production of alcohol beverages is a process that involves the active participation of microorganisms, most often yeasts.

Learning Objectives

- Explain why microorganisms are used for beer, wine, and sake production.

Key Points

- Yeasts are the main fermentor and alcohol producer in the production of wine, beer and other alcohol drinks.
- The main yeast species used is Saccharomyces cerevisiae. It ferments the sugars, coming from different sources, e.g., grapes for wine, barley for beer, to alcohol and carbon dioxide.
- Both wild and cultivated strains are used. The species or strains used in the fermentation play an important role in giving the final taste properties of the drink.

Key Terms

- **must**: The unfermented grape juice of crushed grapes that contains fruit, seeds and skins.

Humans have been producing alcoholic beverages for thousands of years. The production of alcohol in these drinks is based primarily on yeast fermentation. Yeasts are eukaryotic microorganisms that ferment variety of sugars from different sources into the final products of carbon dioxide and alcohol.

Wine production

Wine is made from grapes or other fruit. The grapes are first cleaned of leaves and stems and the fruit is crushed into must that is ready for fermentation. The yeasts used for the fermentation grow a film on the fruit or in the environment. These wild strains play an important role in the final properties of the drink. However, cultivated strains of *Saccharomyces cerevisiae* are often added to improve the consistency of the final product. There are hundreds of commercially available yeast strains for wine fermentation.



Figure: **Wine grapes**: The white film that covers the grapes contains wild yeasts.

In the fermentation process, energy that is converted to heat is produced as well. It is important to keep the temperature in the fermentation vessel lower than 40ºC to keep the yeasts alive. To improve yeast growth, additional nutrients, like diammonium phosphate, are sometimes added in the fermentation step.

When making red wine, there is an additional fermentation step after alcoholic fermentation. Malic acid, naturally present in grape juice, can be converted to lactic acid by lactic acid bacteria naturally found in wineries or added artificially.

Beer production

Beer is the most consumed alcoholic beverage in the world. It is made most often of malted barley and malted wheat. Sometimes a mixture of starch sources can be used, such as rice. Unmalted maize can be added to the barley or wheat to lower cost. Potatoes, millet and other foods high in starch are used in different places in the world as the primary carbohydrate source.

The process of making beer is called brewing. It includes breaking the starch in the grains into a sugary liquid, called wort, and fermenting the sugars in the wort into alcohol and carbon dioxide by yeasts. Two main species are used in the fermentation process: *Saccharomyces cerevisiae* (top-fermenting, since it forms foam on top of the wort) and *Saccharomyces uvarum* (bottom-fermenting). Top-fermenting yeasts are used to produce ale, while bottom-fermenting produce lagers. The temperature used for top-

fermenting (15-24ºC) leads to the production of a lot of esters and flavor products that give beer a fruity taste. Hops are added to introduce a bitter taste and to serve as a preservative.

Brewer's yeasts are very rich in essential minerals and B vitamins, with the exception of vitamin B12. Beer brewing in modern days is performed by added pure cultures of the desired yeast species to the wort. Additional yeasts species that are used in making beer are *Dekkera/Brettanomyces.* After the fermentation is finished, the beer is cleared of the yeasts by precipitation or with the use of clearing additives.

Other types of alcohol beverages are made by the fermentation activity of microorganisms as well. A few examples are sake (uses the fungus *Aspergillus oryzae* to facilitate starch fermentation from rice), brandy, whiskey (both are distilled alcohol), and other alcohol beverages with higher percentage of alcohol compared to wine and beer.

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17.4B: Vinegar

Vinegar is a food product made by acetic acid bacteria that can ferment the alcohol in alcoholic liquids to acetic acid.

Learning Objectives

- Describe how vinegar is made and the common uses of vinegar

Key Points

- The fermentation of alcohol requires oxygen and its availability can determine the rate of vinegar production.
- The main genus used for vinegar fermentation is Acetobacter sp. since the final product of its fermentation can contain acetic acid as high as 20%.
- Some of the most common uses of vinegar are in food preparation, as a cleaning agent, and as a medicine.

Key Terms

- **starter culture**: Starter culture consists of live microorganisms with some medium used to start fermentation or growth in a fresh new medium (substrate).

Vinegar has been used for cooking and in the household and different industries due to its mildly acidic nature for many centuries. It is one of the foods together with beer, wine, bread and fermented dairy products, that is the result of fermentation by microorganisms and has been around for thousands of years. It is a mixture of acetic acid (most often 5%) and water.

The fermentation is performed usually by acetic acid bacteria, from the genus *Acetobacter*, from the alcohol in variety of sources (e.g., apple cider, wine, potatoes, fermented grain). *Acetobacter* bacteria are Gram negative aerobic rods. They are naturally present in environments where alcohol is being produced and can be isolated from damaged fruit, apple cider, etc. In these liquids, the bacteria form a film on the surface, since they are aerobic and need good oxygen supply. This film, called mother of vinegar, can be used as a starter culture of acetic fermentation in fresh alcohol liquids. Mother of vinegar can also be found in unpasteurized store brand vinegar. Acetic acid bacteria are transmitted in nature by vectors like fruit flies and Vinegar eels.



Figure: **Mother of vinegar**: Mother of vinegar is used as a starter culture for vinegar production. It is made of a specific cellulose and acetic acid bacteria

This acetic acid fermentation needs oxygenation. If left at room temperature alcohol containing solution with *Acetobacter* will be converted to vinegar in months. The industrial process can be completed within hours since air is bubbled and mixed through the solution.

Vinegar can also be an undesired product in wine production. If the temperature in the fermentation vessel is too high, the *Acetobacter* will outgrow the yeasts and the produced alcohol will be converted to vinegar.

There are bacteria that can convert sugars straight to acetic acid in anaerobic fermentation. Such species include *Clostridium* and *Acetobacterium* but they can not tolerate acetic acid of concentrations higher than a few percent. The product made from these bacteria must be concentrated while oxidative fermentation by *Acetobacter*can produce up to 20% acetic acid.

Vinegar is a food product made all over the world from many different carbohydrate sources where alcohol fermentation has been performed. Some of them are more commonly used, such as apple cider and grapes, while others such as coconut water, dates, kiwifruit are used in specific regions of the world. Vinegar is used not only in food preparation but also as a cleaning agent due to its acidic nature and strong antibacterial properties. It can be used to lower the glycemic index of foods if consumed together with them. It has also been shown to reduce the risk of fatal ischemic heart disease when consumed frequently with oil in salad dressings.

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17.4C: Citric Acid and Other Organic Compounds

Many organic compounds, like citric acid, are produced industrially by microorganisms.

Learning Objectives

- Explain how citric acid and other organic compounds are produced by the mold *Aspergillus niger*

Key Points

- The major industrial producer of citric acid is the mold Aspergillus niger.
- It has the ability to produce citric acid in high quantities and exports it outside the cells.
- Citric acid is used in the food, chemical and pharmaceutical industries.

Key Terms

- **molasses**: Molasses is viscous syrup produced from a variety of sources, such as sugar beets, sugarcane and grapes.

Citric acid (citrate) is an important substance in the Krebs cycle. It is produced from acetyl coenzyme A and oxaloacetate in the presence of the enzyme citrate synthase. The Krebs cycle is key in the oxidation of sugars, proteins and fats to carbon dioxide and water. Many of the cycle compounds are also needed for the synthesis of the cells' own proteins, carbohydrates, and fats.

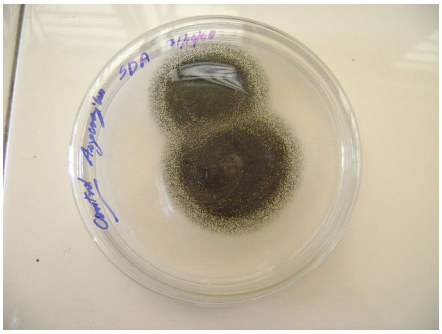

Figure: **Colonies of Aspergillus niger**: The black dots covering the colonies are Aspergillus spores. The growth medium is Saboraud's Dextrose Agar (SDA)

Citrate has been used for centuries in different industries and in the households. It is used as a food additive to give a sour taste to foods or to preserve certain qualities of food products (e.g., prevents separating of the fats in ice cream). It has natural antibacterial properties and is used as a preservative as well. Its buffering property is used in cosmetics and pharmaceuticals to adjust the pH of products.

For centuries, the source of citric acid were citrus fruits. After World War I, the ability of some microorganisms to produce citric acid was further explored and the technology for industrial production was developed. *Penicillium* mold was the first described organism to produce citric acid but industrially another mold, *Aspergillus niger*, became the microorganism of choice. The mold is grown in a medium with sucrose or glucose as the main carbon source. The sugar source is usually an inexpensive solution like molasses or corn steep liquor. The microorganism makes more citric acid in the Krebs cycle than needed for the cell's metabolism and exports it outside the cell. The citric acid is then precipitated out of solution and regenerated.

Microorganisms replaced the industrial chemical production of many different organic compounds, like enzymes and amino acids. Enzymes, such as glucoamylase (used to make high-fructose corn syrup) and pectinase (clearing agent for apple cider and wines) are produced industrially by *Aspergillus. T*he food additivemonosodium glutamate (MSG) is produced in the form of glutamic acid by *Corynebacterium glutamicum*.

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17.4D: Edible Fungi

Fungi are used as food or as producers of a variety of food products (bread, wine, beer, etc.) or compounds used in different industries.

Learning Objectives

- Describe how yeast, molds and mushrooms are used in the food industry

Key Points

- The single cell yeast species, Saccharomyces cerevisiae, has been used as the major leavening agent in making bread for thousands of years.
- Different species of the mold Penicillium are added to milk or curd when making soft cheese to produce blue cheese.
- Mushrooms have fleshy fruit body with certain aroma and flavors as well as good nutritional properties and are used mostly as food.

Key Terms

- **leavening agent**: An organism or compound that can make dough rise and produce soft bread.
- **curd**: Curd is the solid coagulated fraction of milk after it has been digested with enzymes or treated with sour substances.
- **gangrene**: The death of tissue due to reduced blood supply as a result of infection or a blocked blood vessel.

Fungi are eukaryotic organisms that are separated taxonomically in the Fungi kingdom. The kingdom includes yeasts and molds (both microorganisms) and mushrooms. These organisms are ubiquitous all over the world. They have been used by people as food or as producers of a huge variety of food products or compounds used in different industries.

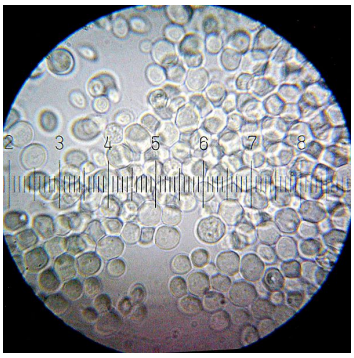

Figure: **Saccharomyces cerevisiae**: Single cells of baker's yeasts under a light microscope. Total magnification is 1,500 x; gradation marks are 1 µm apart

Yeasts

The yeast species *Saccharomyces cerevisiae* has been used as leavening agentfor the production of bread since ancient times. The yeasts ferment the carbohydrates in the dough and produce carbon dioxide that causes the dough to rise and the bread to be softer after baking. Different sources provided the starter cultures. Dough could be left exposed to the air before cooking. Beer foam or grape juice paste were alos used as yeasts sources. Nowadays, the common used starters are pure cultures of *Saccharomyces cerevisiae* produced and sold as baker's yeasts, although some artisan bakers maintain their own starter cultures. Other yeasts and some bacteria can be used as leavening agents too. For example, sourdough is made with *Saccharomyces exiguus* and *Lactobacillus* cultures that give it its sour taste.

Molds

Molds are fungi which cells grow in long chains of filamentous hyphae. The first antibiotic used in modern medicine, penicillin, was isolated form *Penicillium* mold. Different species of the mold *Penicillium* are added to milk or curd when making soft cheese to produce blue cheese. The mold adds specific smell and flavor to the cheese. Some bacteria, such as *Brevibacterium linens*, are also used to give blue cheese its characteristic odor.



Figure: **Boletus edulis**: An edible wild mushroom widely distributed in the Northern Hemisphere and artificially introduced to the Southern Hemisphere

Each mold species is usually found in the environment of the local region where the production of specific brand started. To enhance the mold growth in cheese, different techniques are applied to improve the access of air. The cheese is ripen for weeks to months in dark cold places. Even before the discovery of penicillin, people used blue cheese to prevent gangrene in wounds.

Mushrooms

Edible mushrooms are macrofungi since they are visible with a naked eye. Mushrooms have fleshy fruit body with certain aroma and flavors as well as good nutritional properties and are used mostly as food. A few species of mushrooms have been cultivated but wild mushrooms are harvested as well. However, some mushrooms produce toxic compounds that can be life-threatening. Proper identification is key since quite often poisonous mushrooms mimic edible ones in appearance. Even if not dangerous, mushrooms in general are great absorbants of chemicals from the environment and sometimes they can make them toxic, e.g., pesticides, insecticides, heavy metals. Certain mushrooms have been used for their medicinal properties in some cultures.

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17.4E: Edible Algae

Edible algae have been used as food for centuries in many coastal regions all over the world.

Learning Objectives

- Describe the nutritional value of algae

Key Points

- Algae are a very diverse group of generally simple unicellular or multicellular eukaryotic organisms.
- Algae are of excellent nutritional value since they contain complete protein, fiber, and sometimes high levels of omega-3 fatty acids, many vitamins and minerals.
- Some compounds that are used as additives in the food industry are isolated from algae.

Key Terms

- **complete protein**: Complete protein (whole protein) is a protein that contains all of the nine essential amino acids.

Algae are a very diverse group of generally simple unicellular or multicellular eukaryotic organisms. Most of them are autotrophic which means that they can harvest carbon dioxide from the atmosphere and convert it to organic matter. They inherited their photosynthetic apparatus from cyanobacteria. Cyanobacteria are sometimes called blue-green algae but they are prokaryotic organisms and are not true algae. Some cyanobacterial species are used as food as well.

Seaweeds are edible algae that have been used for centuries as food in many coastal regions all over the world. They may belong to one of three groups of multicellular algae: red, green or brown. In countries such as China, Japan, Korea and to some extent Iceland, Ireland, Chile and New Zealand algae are part of people's regular diet. They are usually of marine origin since freshwater algae are often poisonous.



Figure: **Sea grapes**: Sea grapes (Caulerpa lentillifera) is a type of seaweed consumed raw as a salad or snack

Algae are of excellent nutritional value since they contain complete protein (in contrast to plant food harvested on land), fiber, and sometimes high levels of omega-3 fatty acids. In fact, the omega-3 acids in fish comes from the microalgae consumed at the bottom of the food pyramide and gradually passed up to the fish at the top. Algae are also rich in many vitamins, such as A, C, B_1, B_2, B_3 and B_6, as well as minerals, such as iodine, calcium, potassium, magnesium and iron. They are consumed both cooked, dried and raw.

Cultivated microalgae and cyanobacteria such as *Spirulina* and *Chlorella* are sold as nutritional supplements. Hydrocolloids such as agar, alginate and carrageenan are isolated from wild and cultivated algae and used as additives in the food industry for their emulsifying and thickening properties. Some of the complex polysaccharides found in algae may be digested by bacteria in the gut since the needed enzymes for digestion are abundantly present in Japanese people but absent in people from North America.

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17.4F: Microbes and Dairy Products

Fermented dairy products have been prepared and consumed by people for centuries due to their high nutritional values.

Learning Objectives

- Describe how fermented milk and dairy products are produced and explain their nutritional value

Key Points

- The fermentation is usually performed by lactic acid bacteria which ferment the lactose in milk and convert it to lactic acid leading to precipitation of the proteins.
- There is a tremendous variety of fermented dairy products in many regions in the world. The properties of each product depend on the local strains used for the fermentation.
- Many lactic acid bacteria have also been investigated for medicinal health benefits in the past few decades but so far the results are inconclusive.

Key Terms

- **rennet**: Enzymes derived from mammalian stomachs that contain proteases and lipase.
- **whey**: The remaining liquid after milk curdling.

Fermented milk or dairy products have been part of human diet since ancient times. Various fermented products are made by different strains. Lactic acid fermentation is performed most often by lactic acid bacteria. Due to their abundance in nature, including mucosal surfaces of the human body, and their use in fermented foods they are labeled as GRAS (generally recognized as safe). The main genera that belong to the lactic acid bacteria group are: *Lactobacillus*, *Leuconostoc*, *Lactococcus*, *Pediococcus*and *Streptococcus*. These bacteria ferment the carbohydrates in milk, the major one being lactose, to lactic acid and some other products. The acid precipitates the proteins in the milk and that is why fermented products are usually of thicker consistency than milk. The high acidity and low pH hinders the growth of other bacteria, including pathogens. Some lactic acid bacteria can produce agents with antimicrobial properties. Since milk is rich in many nutrients such as protein, calcium, phosphorus, and B vitamins dairy products are an excellent food.

Some of the most popular and widespread cultured dairy products are yogurt and cheese.

Records of yogurt preparation as food date back to centuries BCE. Classic yogurt is the result of the fermentation of two main bacterial species: *Lactobacillus bulgaricus* and *Streptococcus thermophilus.* Sometimes other lactic acid bacteria are added as well. Yogurt is most often made of cow's milk although milk from sheep, goat, water buffalo, camels and yaks is used as well depending on the region of cultivation.

To make yogurt, the milk is first heated to 80ºC or boiled to kill any pathogenic bacteria and to denature the milk proteins to prevent the formation of curds. After it is cooled down to about 45ºC, the starter culture of the two species is mixed well with the milk and incubated at the same temperature for a few hours. In many countries, the traditional food is yogurt without any sweeteners which could be consumed plain or used to prepare a variety of dishes usually with vegetables. Yogurt has been traditionally consumed in Eastern cultures as a cold drink after mixing with water (e.g., lassi, ayran, doogh). After the industrialization of yogurt production in the twentieth century, yogurt with added sweetener and fruit or fruit jam has become popular in the Western world.



Figure: **Turkish cacik**: A yogurt dish made of plain yogurt and cucumbers.

Cheese is another popular and ancient dairy product. It consists of milk proteins and fat together with lactic acid bacteria. It has longer shelf life than uncultured milk. Currently there are a few hundred varieties of cheese produced all over the world. Making cheese is similar to yogurt but after acidification usually with lactic acid bacteria (*Lactococci*, *Lactobacilli*, *Streptococci*), the solids are separated from the whey by coagulation with rennet and processed further to yield the final product. Depending on the type of cheese, the solids could go straight to packaging or other bacteria or mold could be added (e.g., *Penicillium* mold for blue cheese) for additional fermentation.

Other fermented and widely consumed cultured dairy products include kefir (lactic acid bacteria and yeasts are used for the fermentation), sour cream (fermented cream), cultured buttermilk (fermented cow's milk with *Streptococcus lactis* or *Lactobacillus bulgaricus* only).

Lactic acid bacteria have been researched for medicinal health benefits. In the early twentieth century, the Nobel laureate in medicine, Elie Metchnikoff, believed that the longevity of peasants in Bulgaria and the Russian steppes was due to their high consumption of milk-fermented products. He hypothesized that the lactic acid bacteria would inhabit the gut after consumption, create and acidic environment as they grow and multiply, and hence prevent the growth of proteolytic. After it was discovered that *Lactobacillus bulgaricus* can not live in the human gut, the idea was abandoned. Years later, strains of *Lactobacillus acidophilus* were found to thrive in the gut after implantation and the research started again. The term "probiotics" was introduced and defined as live microorganisms that provide beneficial effects for their host when administered in adequate concentration. Most of the researched species were isolated from different fermented dairy products. The research has been focused on curing or preventing a number of diseases like diarrhea, intestinal inflammations, urogenital infections, allergies, etc. Some species have been prepared and sold as nutritious supplements. However, so far there has not been enough evidence to establish a definite cause and effect relationship about any of the marketed products.

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SECTION OVERVIEW

17.5: Food Preservation

Topic hierarchy

17.5A: Fermented Foods

17.5B: Food Spoilage by Microbes

17.5C: Food Preservation

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17.5A: Fermented Foods

Fermentation is the conversion of carbohydrates to alcohols and carbon dioxide or organic acids using microorganisms.

Learning Objectives

- Describe the process of fermentation and its use in the food industry

Key Points

- Fermentation usually implies that the action of microorganisms is desirable.
- Fermentation produces alcoholic beverages such as wine, beer, and cider.
- Fermentation is also employed in the leavening of bread and the production of dairy products.

Key Terms

- **fermentation**: Fermentation in food processing typically is the conversion of carbohydrates to alcohols and carbon dioxide or organic acids using yeasts, bacteria, or a combination thereof, under anaerobic conditions.
- **carbohydrates**: A major class of foods that includes sugars and starches.
- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **oligodynamic action**: that is active in small quantities; used especially to describe the sterilizing effect of some heavy metals against bacteria

Fermentation in food processing typically is the conversion of carbohydrates to alcohols and carbon dioxide or organic acids using yeasts, bacteria, or a combination thereof, under anaerobic conditions. Fermentation in simple terms is the chemical conversion of sugars into ethanol. The science of fermentation is also known as zymology or zymurgy.

Historically, when studying the fermentation of sugar to alcohol by yeast, Louis Pasteur concluded that the fermentation was catalyzed by a vital force, called “ferments,” within the yeast cells. The “ferments” were thought to function only within living organisms. “Alcoholic fermentation is an act correlated with the life and organization of the yeast cells, not with the death or putrefaction of the cells,” he wrote.

Fermentation usually implies that the action of microorganisms is desirable. This process is used to produce alcoholic beverages such as wine, beer, and cider. Fermentation is also employed in the leavening of bread (CO_2 produced by yeast activity); in preservation techniques to produce lactic acid in sour foods such as sauerkraut, dry sausages, kimchi, and yogurt; and in the pickling of foods with vinegar (acetic acid).



Figure: **Beer**: This is beer fermenting at a brewery.

Food fermentation has been said to serve five main purposes:

1. Enrichment of the diet through development of a diversity of flavors, aromas, and textures in food substrates.
2. Preservation of substantial amounts of food through lactic acid, alcohol, acetic acid, and alkaline fermentations.
3. Biological enrichment of food substrates with protein, essential amino acids, essential fatty acids, and vitamins.
4. Elimination of antinutrients.
5. A decrease in cooking time and fuel requirement.

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17.5B: Food Spoilage by Microbes

Food spoilage is the process in which food deteriorates to the point it is not edible to humans or its quality of edibility becomes reduced.

Learning Objectives

- Describe the process of food spoilage

Key Points

- Bacteria can cause food spoilage by breaking down the food, producing acids or other waste products during this process.
- Harvested crops decompose from the moment they are harvested due to attacks from microorganisms.
- Signs of food spoilage may include an appearance different from the food in its fresh form, such as a change in color, a change in texture, an unpleasant odor, or an undesirable taste.

Key Terms

- **food spoilage**: Food spoilage is the process in which food deteriorates to the point that it is not edible to humans or its quality of edibility becomes reduced.
- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **bacteria**: A type, species, or strain of bacterium.

Food spoilage is the process in which food deteriorates to the point that it is not edible to humans or its quality of edibility becomes reduced. Various external forces are responsible for the spoilage of food. Food that is capable of spoiling is referred to as perishable food.



Figure: **Food Spoilage**: This apple has decomposed to the point that it is unappealing for humans to eat.

Harvested crops decompose from the moment they are harvested due to attacks from microorganisms.

Various bacteria can be responsible for the spoilage of food. When bacteria breaks down the food, acids and other waste products are created in the process. While the bacteria itself may or may not be harmful, the waste products may be unpleasant to taste or may even be harmful to one's health.

Yeasts can be responsible for the decomposition of food with a high sugar content. The same effect is useful in the production of various types of food and beverages, such as bread, yogurt, cider, and alcoholic beverages.

Signs of food spoilage may include an appearance different from the food in its fresh form, such as a change in color, a change in texture, an unpleasant odor, or an undesirable taste. The item may become softer than normal. If mold occurs, it is often visible externally on the item.

Some spoiled foods are harmless to eat, and may simply be diminished in quality. But foods exhibiting certain types of spoilage may be harmful to consume. Uncooked or under-cooked animal flesh that spoils is typically quite toxic, and consumption can result in serious illness or death. The toxic effects from consuming spoiled food are known colloquially as "food poisoning", and more properly as "foodborne illness. "

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17.5C: Food Preservation

Food preservation is the process of treating food to stop or slow down spoilage, loss of quality, edibility, or nutritional value.

Learning Objectives

- Describe how food preservation processes stop or slow down food spoilage thus allowing for longer food storage

Key Points

- Preservation usually involves preventing the growth of bacteria, fungi (such as yeasts), and other microorganisms, as well as retarding the oxidation of fats which cause rancidity.
- A number of methods of prevention can be used that can either totally prevent, delay, or otherwise reduce food spoilage.
- Maintaining or creating nutritional value, texture, and flavor is an important aspect of food preservation.

Key Terms

- **Preservation**: Food preservation is the process of treating and handling food to stop or slow down food spoilage, loss of quality, edibility, or nutritional value and thus allow for longer food storage.
- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **food spoilage**: Spoilage is the process in which food deteriorates to the point that it is not edible to humans or its quality of edibility becomes reduced.

Food Preservation

Food preservation is the process of treating and handling food to stop or slow down food spoilage, loss of quality, edibility, or nutritional value and thus allow for longer food storage.

Preservation usually involves preventing the growth of bacteria, fungi (such as yeasts), and other microorganisms, as well as retarding the oxidation of fats which cause rancidity.

Methods of Food Preservation

A number of methods of prevention can be used that can either totally prevent, delay, or otherwise reduce food spoilage. Preservatives can expand the shelf life of food and can lengthen the time long enough for it to be harvested, processed, sold, and kept in the consumer's home for a reasonable length of time.

Maintaining or creating nutritional value, texture and flavor is an important aspect of food preservation, although, historically, some methods drastically altered the character of the food being preserved. In many cases these changes have now come to be seen as desirable qualities, as with cheese, yogurt, and pickled onions.

Drying is one of the most ancient food preservation techniques, which reduces water activity sufficiently to prevent bacterial growth.

Refrigeration preserves food by slowing down the growth and reproduction of microorganisms and the action of enzymes which cause food to rot.

Freezing is also one of the most commonly used processes for preserving a very wide range of food including prepared foodstuffs which would not have required freezing in their unprepared state.

Vacuum-packing stores food in a vacuum environment, usually in an air-tight bag or bottle. The vacuum environment strips bacteria of oxygen needed for survival, thereby slowing spoiling. Vacuum-packing is commonly used for storing nuts to reduce the loss of flavor from oxidation.

Salting or curing draws moisture from the meat through a process of osmosis. Meat is cured with salt or sugar, or a combination of the two. Nitrates and nitrites are also often used to cure meat and contribute to the characteristic pink color, as well as inhibition of Clostridium botulinum.

Sugar is used to preserve fruits, either in syrup with fruit such as apples, pears, peaches, apricots, plums, or in crystallized form where the preserved material is cooked in sugar to the point of crystallisation and the resultant product is then stored dry. This

method is used for the skins of citrus fruit (candied peel), angelica, and ginger. A modification of this process produces glacé fruit such as glacé cherries where the fruit is preserved in sugar but is then extracted from the syrup and sold, the preservation being maintained by the sugar content of the fruit and the superficial coating of syrup. The use of sugar is often combined with alcohol for preservation of luxury products such as fruit in brandy or other spirits. These should not be confused with fruit flavored spirits such as cherry brandy.

Smoking is used to lengthen the shelf life of perishable food items. This effect is achieved by exposing the food to smoke from burning plant materials such as wood. Most commonly subjected to this method of food preservation are meats and fish that have undergone curing. Fruits and vegetables like paprika, cheeses, spices, and ingredients for making drinks such as malt and tea leaves are also smoked, but mainly for cooking or flavoring them. It is one of the oldest food preservation methods, which probably arose after the development of cooking with fire.

Preservative food additives can be antimicrobial. These inhibit the growth of bacteria or fungi, including mold, or antioxidant, such as oxygen absorbers, which inhibit the oxidation of food constituents. Common antimicrobial preservatives include calcium propionate, sodium nitrate, sodium nitrite, sulfites (sulfur dioxide, sodium bisulfite, potassium hydrogen sulfite, etc.), and disodium EDTA. Antioxidants include BHA and BHT. Other preservatives include formaldehyde (usually in solution), glutaraldehyde (kills insects), ethanol, and methylchloroisothiazolinone.

Pickling is a method of preserving food in an edible anti-microbial liquid. Pickling can be broadly categorized into two categories: chemical pickling and fermentation pickling.

Canning involves cooking food, sealing it in sterile cans or jars, and boiling the containers to kill or weaken any remaining bacteria as a form of sterilization. Foods have varying degrees of natural protection against spoilage and may require that the final step occur in a pressure cooker. High-acid fruits like strawberries require no preservatives to can and only a short boiling cycle, whereas marginal fruits such as tomatoes require longer boiling and addition of other acidic elements. Low acid foods, such as vegetables and meats require pressure canning. Food preserved by canning or bottling is at immediate risk of spoilage once the can or bottle has been opened.



Figure: **Preserved Food**: Canning food is one method of food preservation.

Other forms of preservation can include: jellying, jugging, irradiation, pulsed electric field processing, modified atmosphere, high pressure, burial in the ground, and biopreservation.

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2.1.2: Electronic Orbitals
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SECTION OVERVIEW

2.1: Atomic Structure

Topic hierarchy

2.1.1: Overview of Atomic Structure

2.1.2: Electronic Orbitals

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2.1.1: Overview of Atomic Structure

Atoms are made up of particles called protons, neutrons, and electrons, which are responsible for the mass and charge of atoms.

Learning Objectives

- Discuss the electronic and structural properties of an atom

Key Points

- An atom is composed of two regions: the nucleus, which is in the center of the atom and contains protons and neutrons, and the outer region of the atom, which holds its electrons in orbit around the nucleus.
- Protons and neutrons have approximately the same mass, about 1.67 × 10-24 grams, which scientists define as one atomic mass unit (amu) or one Dalton.
- Each electron has a negative charge (-1) equal to the positive charge of a proton (+1).
- Neutrons are uncharged particles found within the nucleus.

Key Terms

- **atom**: The smallest possible amount of matter which still retains its identity as a chemical element, consisting of a nucleus surrounded by electrons.
- **proton**: Positively charged subatomic particle forming part of the nucleus of an atom and determining the atomic number of an element. It weighs 1 amu.
- **neutron**: A subatomic particle forming part of the nucleus of an atom. It has no charge. It is equal in mass to a proton or it weighs 1 amu.

An atom is the smallest unit of matter that retains all of the chemical properties of an element. Atoms combine to form molecules, which then interact to form solids, gases, or liquids. For example, water is composed of hydrogen and oxygen atoms that have combined to form water molecules. Many biological processes are devoted to breaking down molecules into their component atoms so they can be reassembled into a more useful molecule.

Atomic Particles

Atoms consist of three basic particles: protons, electrons, and neutrons. The nucleus (center) of the atom contains the protons (positively charged) and the neutrons (no charge). The outermost regions of the atom are called electron shells and contain the electrons (negatively charged). Atoms have different properties based on the arrangement and number of their basic particles.

The hydrogen atom (H) contains only one proton, one electron, and no neutrons. This can be determined using the atomic number and the mass number of the element (see the concept on atomic numbers and mass numbers).

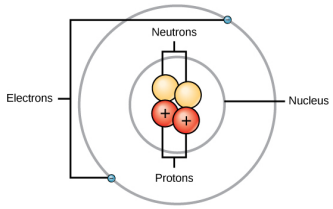


Figure: **Structure of an atom**: Elements, such as helium, depicted here, are made up of atoms. Atoms are made up of protons and neutrons located within the nucleus, with electrons in orbitals surrounding the nucleus.

Atomic Mass

Protons and neutrons have approximately the same mass, about 1.67×10^{-24} grams. Scientists define this amount of mass as one atomic mass unit (amu) or one Dalton. Although similar in mass, protons are positively charged, while neutrons have no charge. Therefore, the number of neutrons in an atom contributes significantly to its mass, but not to its charge.

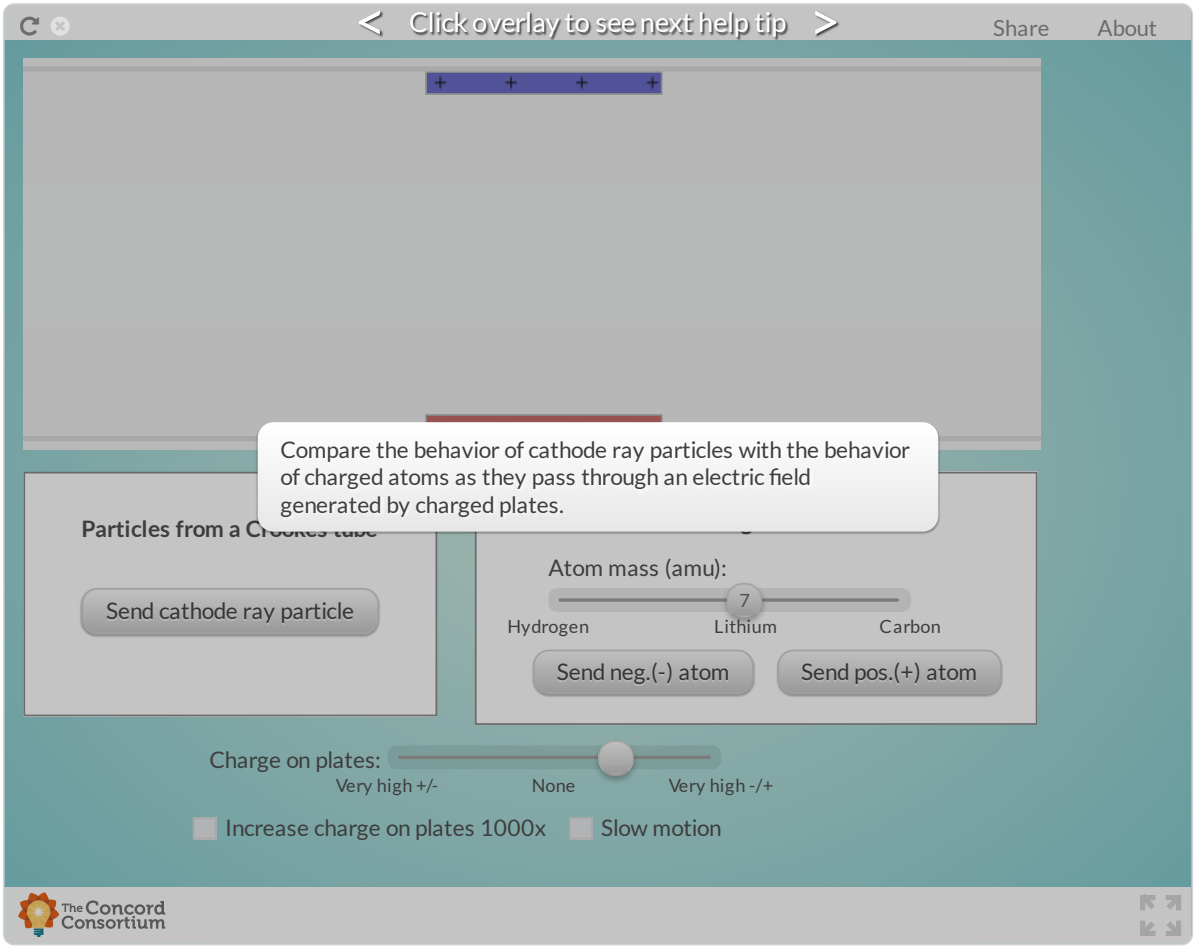
Electrons are much smaller in mass than protons, weighing only 9.11×10^{-28}grams, or about 1/1800 of an atomic mass unit. Therefore, they do not contribute much to an element's overall atomic mass. When considering atomic mass, it is customary to ignore the mass of any electrons and calculate the atom's mass based on the number of protons and neutrons alone.

Electrons contribute greatly to the atom's charge, as each electron has a negative charge equal to the positive charge of a proton. Scientists define these charges as "+1" and "-1. " In an uncharged, neutral atom, the number of electrons orbiting the nucleus is equal to the number of protons inside the nucleus. In these atoms, the positive and negative charges cancel each other out, leading to an atom with no net charge.

Protons, Neutrons, and Electrons			
	Charge	**Mass (amu)**	**Location**
Proton	+1	1	nucleus
Neutron	0	1	nucleus
Electron	–1	0	orbitals

Figure: **Protons, neutrons, and electrons**: Both protons and neutrons have a mass of 1 amu and are found in the nucleus. However, protons have a charge of +1, and neutrons are uncharged. Electrons have a mass of approximately 0 amu, orbit the nucleus, and have a charge of -1.

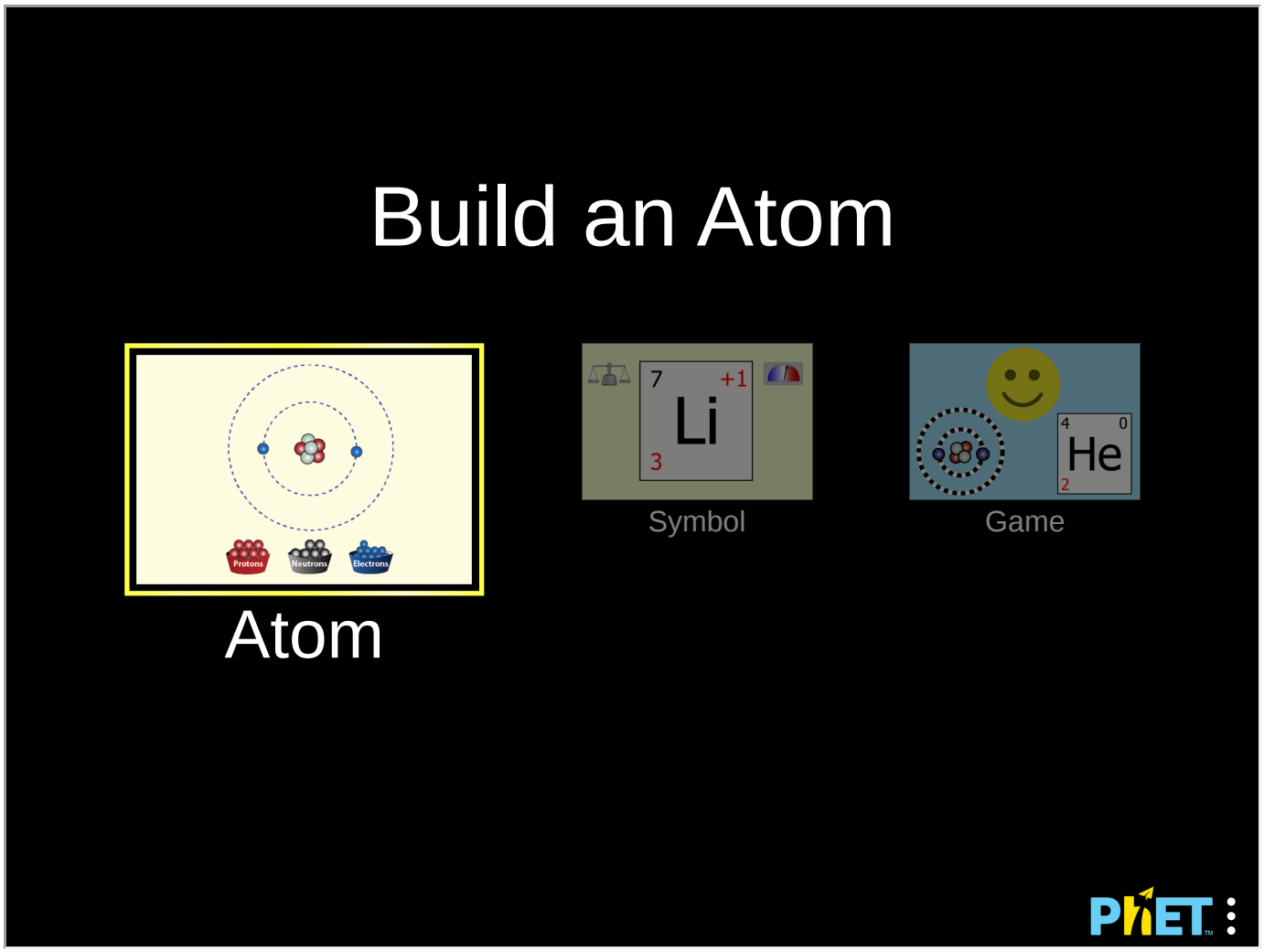
Exploring Electron Properties: Compare the behavior of electrons to that of other charged particles to discover properties of electrons such as charge and mass.



Volume of Atoms

Accounting for the sizes of protons, neutrons, and electrons, most of the volume of an atom—greater than 99 percent—is, in fact, empty space. Despite all this empty space, solid objects do not just pass through one another. The electrons that surround all atoms are negatively charged and cause atoms to repel one another, preventing atoms from occupying the same space. These intermolecular forces prevent you from falling through an object like your chair.

Interactive: Build an Atom: Build an atom out of protons, neutrons, and electrons, and see how the element, charge, and mass change. Then play a game to test your ideas!



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2.1.2: Electronic Orbitals

Electron orbitals are three-dimensional representations of the space in which an electron is likely to be found.

Learning Objectives

- Distinguish between electron orbitals in the Bohr model versus the quantum mechanical orbitals

Key Points

- The Bohr model of the atom does not accurately reflect how electrons are spatially distributed around the nucleus as they do not circle the nucleus like the earth orbits the sun.
- The electron orbitals are the result of mathematical equations from quantum mechanics known as wave functions and can predict within a certain level of probability where an electron might be at any given time.
- The number and type of orbitals increases with increasing atomic number, filling in various electron shells.
- The area where an electron is most likely to be found is called its orbital.

Key Terms

- **electron shell**: The collective states of all electrons in an atom having the same principal quantum number (visualized as an orbit in which the electrons move).
- **orbital**: A specification of the energy and probability density of an electron at any point in an atom or molecule.

Although useful to explain the reactivity and chemical bonding of certain elements, the Bohr model of the atom does not accurately reflect how electrons are spatially distributed surrounding the nucleus. They do not circle the nucleus like the earth orbits the sun, but are rather found in electron orbitals. These relatively complex shapes result from the fact that electrons behave not just like particles, but also like waves. Mathematical equations from quantum mechanics known as wave functions can predict within a certain level of probability where an electron might be at any given time. The area where an electron is most likely to be found is called its orbital.

First Electron Shell

The closest orbital to the nucleus, called the 1s orbital, can hold up to two electrons. This orbital is equivalent to the innermost electron shell of the Bohr model of the atom. It is called the 1s orbital because it is spherical around the nucleus. The 1s orbital is always filled before any other orbital. Hydrogen has one electron; therefore, it has only one spot within the 1s orbital occupied. This is designated as $1s^1$, where the superscripted 1 refers to the one electron within the 1s orbital. Helium has two electrons; therefore, it can completely fill the 1s orbital with its two electrons. This is designated as $1s^2$, referring to the two electrons of helium in the 1s orbital. On the periodic table, hydrogen and helium are the only two elements in the first row (period); this is because they are the sole elements to have electrons only in their first shell, the 1s orbital.

Second Electron Shell

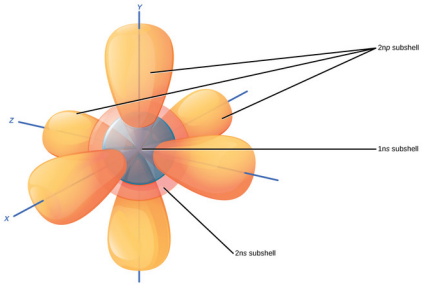

Figure: **Diagram of the S and P orbitals**: The s subshells are shaped like spheres. Both the 1n and 2n principal shells have an s orbital, but the size of the sphere is larger in the 2n orbital. Each sphere is a single orbital. p subshells are made up of three dumbbell-shaped orbitals. Principal shell 2n has a p subshell, but shell 1 does not.

The second electron shell may contain eight electrons. This shell contains another spherical s orbital and three “dumbbell” shaped p orbitals, each of which can hold two electrons. After the 1s orbital is filled, the second electron shell is filled, first filling its 2s orbital and then its three p orbitals. When filling the p orbitals, each takes a single electron; once each p orbital has an electron, a second may be added. Lithium (Li) contains three electrons that occupy the first and second shells. Two electrons fill the 1s orbital,

and the third electron then fills the 2s orbital. Its electron configuration is $1s^2 2s^1$. Neon (Ne), on the other hand, has a total of ten electrons: two are in its innermost 1s orbital, and eight fill its second shell (two each in the 2s and three p orbitals). Thus, it is an inert gas and energetically stable: it rarely forms a chemical bond with other atoms.

Third Electron Shell

Larger elements have additional orbitals, making up the third electron shell. Subshells d and f have more complex shapes and contain five and seven orbitals, respectively. Principal shell 3n has s, p, and d subshells and can hold 18 electrons. Principal shell 4n has s, p, d, and f orbitals and can hold 32 electrons. Moving away from the nucleus, the number of electrons and orbitals found in the energy levels increases. Progressing from one atom to the next in the periodic table, the electron structure can be worked out by fitting an extra electron into the next available orbital. While the concepts of electron shells and orbitals are closely related, orbitals provide a more accurate depiction of the electron configuration of an atom because the orbital model specifies the different shapes and special orientations of all the places that electrons may occupy.

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SECTION OVERVIEW

2.2: Chemical Bonds

Topic hierarchy

2.2.1: Ions and Ionic Bonds

2.2.2: Colvalent Bonds and Other Bonds and Interaction

2.2.3: Hydrogen Bonding

2.2.4: Avogadro's Number and the Mole

2.2.5: Average Atomic Mass

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2.2.1: Ions and Ionic Bonds

Ionic bonds are attractions between oppositely charged atoms or groups of atoms where electrons are donated and accepted.

Learning Objectives

- Predict whether a given element will more likely form a cation or an anion

Key Points

- Ions form from elements when they gain or lose an electron causing the number of protons to be unequal to the number of electrons, resulting in a net charge.
- If there are more electrons than protons (from an element gaining one or more electrons), the ion is negatively charged and called an anion.
- If there are more protons than electrons (via loss of electrons), the ion is positively charged and is called a cation.
- Ionic bonds result from the interaction between a positively charged cation and a negatively charged anion.

Key Terms

- **ion**: An atom, or group of atoms, bearing an electrical charge, such as the sodium and chlorine atoms in a salt solution.
- **ionic bond**: A strong chemical bond caused by the electrostatic attraction between two oppositely charged ions.

Ions and Ionic Bonds

Some atoms are more stable when they gain or lose an electron (or possibly two) and form ions. This results in a full outermost electron shell and makes them energetically more stable. Now, because the number of electrons does not equal the number of protons, each ion has a net charge. Cations are positive ions that are formed by losing electrons (as the number of protons is now greater than the number of electrons). Negative ions are formed by gaining electrons and are called anions (wherein there are more electrons than protons in a molecule). Anions are designated by their elemental name being altered to end in “-ide”. For example, the anion of chlorine is called chloride, and the anion of sulfur is called sulfide.

This movement of electrons from one element to another is referred to as electron transfer. As illustrated, sodium (Na) only has one electron in its outer electron shell. It takes less energy for sodium to donate that one electron than it does to accept seven more electrons to fill the outer shell. When sodium loses an electron, it will have 11 protons, 11 neutrons, and only 10 electrons. This leaves it with an overall charge of +1 since there are now more protons than electrons. It is now referred to as a sodium ion. Chlorine (Cl) in its lowest energy state (called the ground state) has seven electrons in its outer shell. Again, it is more energy efficient for chlorine to gain one electron than to lose seven. Therefore, it tends to gain an electron to create an ion with 17 protons, 17 neutrons, and 18 electrons. This gives it a net charge of -1 since there are now more electrons than protons. It is now referred to as a chloride ion. In this example, sodium will donate its one electron to empty its shell, and chlorine will accept that electron to fill its shell. Both ions now satisfy the octet rule and have complete outer shells. These transactions can normally only take place simultaneously; in order for a sodium atom to lose an electron, it must be in the presence of a suitable recipient like a chlorine atom.

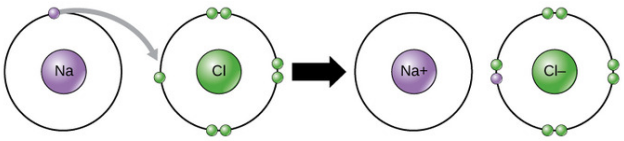

Figure: **Electron Transfer Between Na and Cl**: In the formation of an ionic compound, metals lose electrons and nonmetals gain electrons to achieve an octet. In this example, sodium loses one electron to empty its shell and chlorine accepts that electron to fill its shell.

Ionic bonds are formed between ions with opposite charges. For instance, positively charged sodium ions and negatively charged chloride ions bond together to form sodium chloride, or table salt, a crystalline molecule with zero net charge. The attractive force holding the two atoms together is called the electromagnetic force and is responsible for the attraction between oppositely charged ions.

Certain salts are referred to in physiology as electrolytes (including sodium, potassium, and calcium). Electrolytes are ions necessary for nerve impulse conduction, muscle contractions, and water balance. Many sports drinks and dietary supplements

provide these ions to replace those lost from the body via sweating during exercise.

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2.2.2: Colvalent Bonds and Other Bonds and Interaction

Covalent bonds result from a sharing of electrons between two atoms and hold most biomolecules together.

Learning Objectives

- Compare the relative strength of different types of bonding interactions

Key Points

- A polar covalent bond arises when two atoms of different electronegativity share two electrons unequally.
- A non-polar covalent bond is one in which the electrons are shared equally between two atoms.
- Hydrogen bonds and Van Der Waals are responsible for the folding of proteins, the binding of ligands to proteins, and many other processes between molecules.

Key Terms

- **hydrogen bond**: A weak bond in which a hydrogen atom in one molecule is attracted to an electronegative atom (usually nitrogen or oxygen) in the same or different molecule.
- **covalent bond**: A type of chemical bond where two atoms are connected to each other by the sharing of two or more electrons.
- **dipole**: Any object (such as a magnet, polar molecule or antenna), that is oppositely charged at two points (or poles).

Covalent Bonds and Other Bonds and Interactions

The octet rule can be satisfied by the sharing of electrons between atoms to form covalent bonds. These bonds are stronger and much more common than are ionic bonds in the molecules of living organisms. Covalent bonds are commonly found in carbon-based organic molecules, such as DNA and proteins. Covalent bonds are also found in inorganic molecules such as H_2O, CO_2, and O_2. One, two, or three pairs of electrons may be shared between two atoms, making single, double, and triple bonds, respectively. The more covalent bonds between two atoms, the stronger their connection. Thus, triple bonds are the strongest.

The strength of different levels of covalent bonding is one of the main reasons living organisms have a difficult time in acquiring nitrogen for use in constructing nitrogenous molecules, even though molecular nitrogen, N_2, is the most abundant gas in the atmosphere. Molecular nitrogen consists of two nitrogen atoms triple bonded to each other. The resulting strong triple bond makes it difficult for living systems to break apart this nitrogen in order to use it as constituents of biomolecules, such as proteins, DNA, and RNA.

The formation of water molecules is an example of covalent bonding. The hydrogen and oxygen atoms that combine to form water molecules are bound together by covalent bonds. The electron from the hydrogen splits its time between the incomplete outer shell of the hydrogen atom and the incomplete outer shell of the oxygen atom. In return, the oxygen atom shares one of its electrons with the hydrogen atom, creating a two-electron single covalent bond. To completely fill the outer shell of oxygen, which has six electrons in its outer shell, two electrons (one from each hydrogen atom) are needed. Each hydrogen atom needs only a single electron to fill its outer shell, hence the well-known formula H_2O. The electrons that are shared between the two elements fill the outer shell of each, making both elements more stable.

Polar Covalent Bonds

There are two types of covalent bonds: polar and nonpolar. In a polar covalent bond, the electrons are unequally shared by the atoms because they are more attracted to one nucleus than the other. The relative attraction of an atom to an electron is known as its electronegativity: atoms that are more attracted to an electron are considered to be more electronegative. Because of the unequal distribution of electrons between the atoms of different elements, a slightly positive (δ+) or slightly negative (δ-) charge develops. This partial charge is known as a dipole; this is an important property of water and accounts for many of its characteristics. The dipole in water occurs because oxygen has a higher electronegativity than hydrogen, which means that the shared electrons spend more time in the vicinity of the oxygen nucleus than they do near the nucleus of the hydrogen atoms.

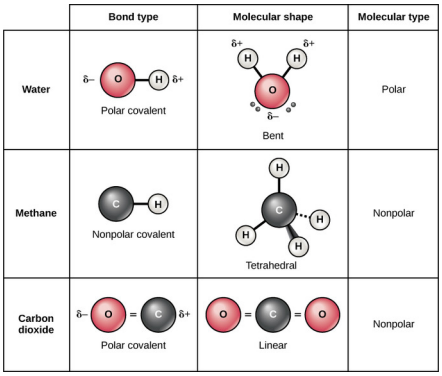


Figure: **Polar and Nonpolar Covalent Bonds**: Whether a molecule is polar or nonpolar depends both on bond type and molecular shape. Both water and carbon dioxide have polar covalent bonds, but carbon dioxide is linear, so the partial charges on the molecule cancel each other out.

Nonpolar Covalent Bonds

Nonpolar covalent bonds form between two atoms of the same element or between different elements that share electrons equally. For example, molecular oxygen (O_2) is nonpolar because the electrons will be equally distributed between the two oxygen atoms. The four bonds of methane are also considered to be nonpolar because the electronegativies of carbon and hydrogen are nearly identical.

Hydrogen Bonds and Van Der Waals Interactions

Not all bonds are ionic or covalent; weaker bonds can also form between molecules. Two types of weak bonds that frequently occur are hydrogen bonds and van der Waals interactions. Without these two types of bonds, life as we know it would not exist.

Hydrogen bonds provide many of the critical, life-sustaining properties of water and also stabilize the structures of proteins and DNA, the building block of cells. When polar covalent bonds containing hydrogen are formed, the hydrogen atom in that bond has a slightly positive charge (δ+) because the shared electrons are pulled more strongly toward the other element and away from the hydrogen atom. Because the hydrogen has a slightly positive charge, it's attracted to neighboring negative charges. The weak interaction between the δ+ charge of a hydrogen atom from one molecule and the δ- charge of a more electronegative atom is called a hydrogen bond. Individual hydrogen bonds are weak and easily broken; however, they occur in very large numbers in water and in organic polymers, and the additive force can be very strong. For example, hydrogen bonds are responsible for zipping together the DNA double helix.

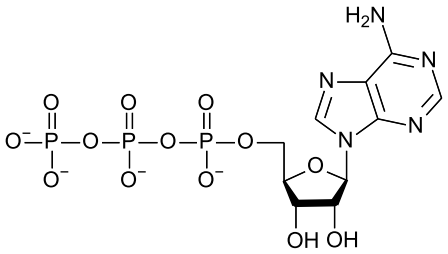
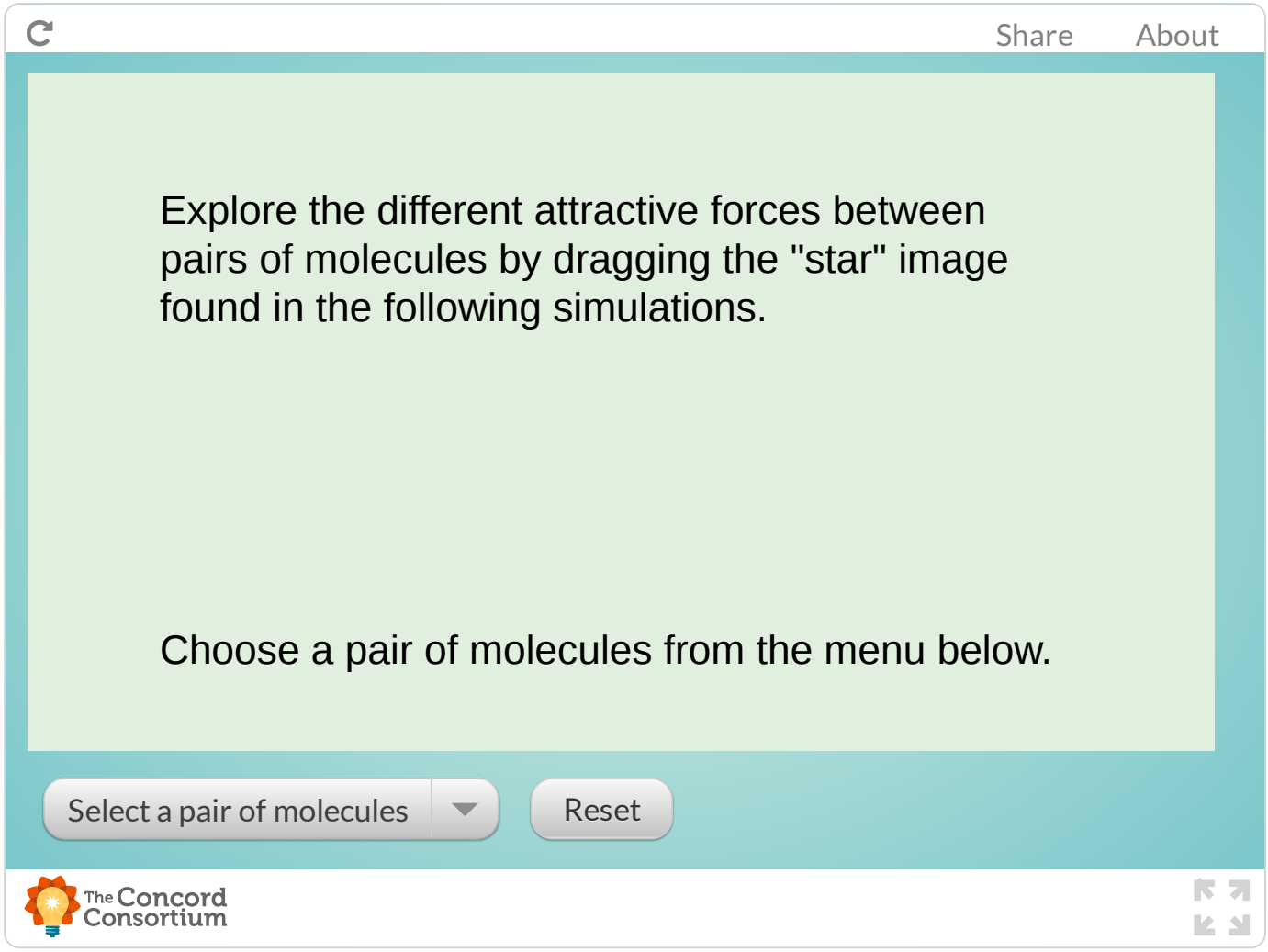


Figure: **Adenosine Triphosphate, ATP**: Adenosine Triphosphate, or ATP, is the most commonly used cofactor in nature. Its biosynthesis involves the fixation of nitrogen to provide feedstocks that eventually produce the carbon-nitrogen bonds it contains.

Like hydrogen bonds, van der Waals interactions are weak interactions between molecules. Van der Waals attractions can occur between any two or more molecules and are dependent on slight fluctuations of the electron densities, which can lead to slight temporary dipoles around a molecule. For these attractions to happen, the molecules need to be very close to one another. These bonds, along with hydrogen bonds, help form the three-dimensional structures of the proteins in our cells that are required for their proper function.

Interactions between different types of molecules: In this interactive, you can explore how different types of molecules interact with each other based on their bonds.



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2.2.3: Hydrogen Bonding

A hydrogen bond is a strong intermolecular force created by the relative positivity of hydrogen atoms.

Learning Objectives

- Describe the properties of hydrogen bonding.

Key Points

- Hydrogen bonds are strong intermolecular forces created when a hydrogen atom bonded to an electronegative atom approaches a nearby electronegative atom.
- Greater electronegativity of the hydrogen bond acceptor will lead to an increase in hydrogen-bond strength.
- The hydrogen bond is one of the strongest intermolecular attractions, but weaker than a covalent or an ionic bond.
- Hydrogen bonds are responsible for holding together DNA, proteins, and other macromolecules.

Key Terms

- **electronegativity**: The tendency of an atom or molecule to draw electrons towards itself, form dipoles, and thus form bonds.
- **hydrogen bond**: The attraction between a partially positively charged hydrogen atom attached to a highly electronegative atom (such as nitrogen, oxygen, or fluorine) and another nearby electronegative atom.
- **intermolecular**: A type of interaction between two different molecules.

Forming a Hydrogen Bond

A hydrogen bond is the electromagnetic attraction created between a partially positively charged hydrogen atom attached to a highly electronegative atom and another nearby electronegative atom. A hydrogen bond is a type of dipole-dipole interaction; it is not a true chemical bond. These attractions can occur between molecules (*inter*molecularly) or within different parts of a single molecule (*intra*molecularly).

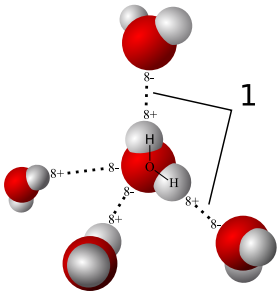


Figure: **Hydrogen bonding in water**: This is a space-filling ball diagram of the interactions between separate water molecules.

Hydrogen Bond Donor

A hydrogen atom attached to a relatively electronegative atom is a hydrogen bond donor. This electronegative atom is usually fluorine, oxygen, or nitrogen. The electronegative atom attracts the electron cloud from around the hydrogen nucleus and, by decentralizing the cloud, leaves the hydrogen atom with a positive partial charge. Because of the small size of hydrogen relative to other atoms and molecules, the resulting charge, though only partial, is stronger. In the molecule ethanol, there is one hydrogen atom bonded to an oxygen atom, which is very electronegative. This hydrogen atom is a hydrogen bond donor.

Hydrogen Bond Acceptor

A hydrogen bond results when this strong partial positive charge attracts a lone pair of electrons on another atom, which becomes the hydrogen bond acceptor. An electronegative atom such as fluorine, oxygen, or nitrogen is a hydrogen bond acceptor, regardless of whether it is bonded to a hydrogen atom or not. Greater electronegativity of the hydrogen bond acceptor will create a stronger hydrogen bond. The diethyl ether molecule contains an oxygen atom that is not bonded to a hydrogen atom, making it a hydrogen bond acceptor.

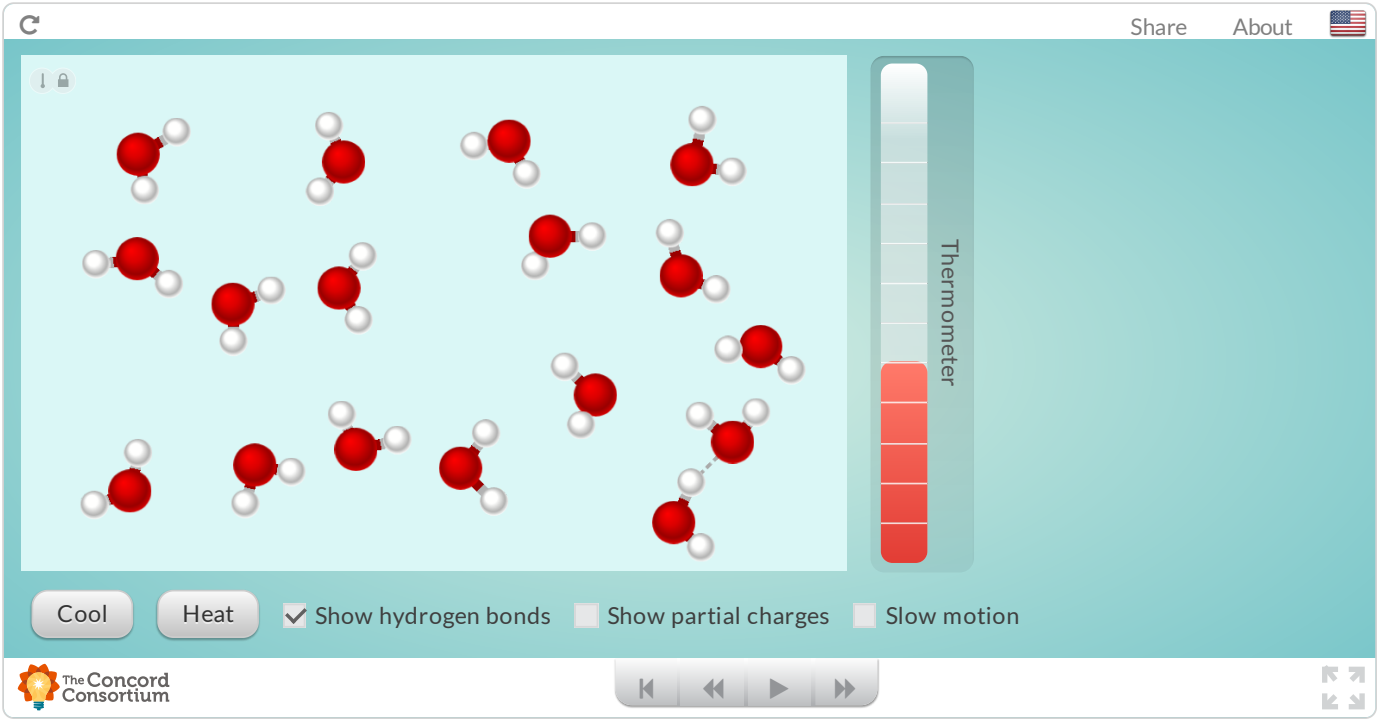
image

Hydrogen bond donor and hydrogen bond acceptor: Ethanol contains a hydrogen atom that is a hydrogen bond donor because it is bonded to an electronegative oxygen atom, which is very electronegative, so the hydrogen atom is slightly positive. Diethyl ether contains an oxygen atom that is a hydrogen bond acceptor because it is not bonded to a hydrogen atom and so is slightly negative.

A hydrogen attached to carbon can also participate in hydrogen bonding when the carbon atom is bound to electronegative atoms, as is the case in chloroform ($CHCl_3$). As in a molecule where a hydrogen is attached to nitrogen, oxygen, or fluorine, the electronegative atom attracts the electron cloud from around the hydrogen nucleus and, by decentralizing the cloud, leaves the hydrogen atom with a positive partial charge.

Interactive: Hydrogen Bonding: Explore hydrogen bonds forming between polar molecules, such as water. Hydrogen bonds are shown with dotted lines. Show partial charges and run the model. Where do hydrogen bonds form? Try changing the temperature of the model. How does the pattern of

hydrogen bonding explain the lattice that makes up ice crystals?



Applications for Hydrogen Bonds

Hydrogen bonds occur in inorganic molecules, such as water, and organic molecules, such as DNA and proteins. The two complementary strands of DNA are held together by hydrogen bonds between complementary nucleotides (A&T, C&G). Hydrogen bonding in water contributes to its unique properties, including its high boiling point (100 °C) and surface tension.



Figure: **Water droplets on a leaf**: The hydrogen bonds formed between water molecules in water droplets are stronger than the other intermolecular forces between the water molecules and the leaf, contributing to high surface tension and distinct water droplets.

In biology, intramolecular hydrogen bonding is partly responsible for the secondary, tertiary, and quaternary structures of proteins and nucleic acids. The hydrogen bonds help the proteins and nucleic acids form and maintain specific shapes.

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2.2.4: Avogadro's Number and the Mole

The mole is represented by Avogadro's number, which is 6.022×10^{23} atoms or molecules per mol.

Learning Objectives

- Define and memorize Avogadro's number

Key Points

- The mole allows scientists to calculate the number of elementary entities (usually atoms or molecules) in a certain mass of a given substance.
- Avogadro's number is an absolute number: there are 6.022×10^{23}elementary entities in 1 mole. This can also be written as $6.022 \times 10^{23}\text{mol}^{-1}$.
- The mass of one mole of a substance is equal to that substance's molecular weight. For example, the mean molecular weight of water is 18.015 atomic mass units (amu), so one mole of water weight 18.015 grams.

Key Terms

- **mole**: The amount of substance of a system that contains as many elementary entities as there are atoms in 12 g of carbon-12.

The chemical changes observed in any reaction involve the rearrangement of billions of atoms. It is impractical to try to count or visualize all these atoms, but scientists need some way to refer to the entire quantity. They also need a way to compare these numbers and relate them to the weights of the substances, which they *can* measure and observe. The solution is the concept of the mole, which is very important in quantitative chemistry.

Avogadro's Number

Amadeo Avogadro first proposed that the volume of a gas at a given pressure and temperature is proportional to the number of atoms or molecules, regardless of the type of gas. Although he did not determine the exact proportion, he is credited for the idea.



Figure: **Amedeo Avogadro**: Amedeo Avogadro is credited with the idea that the number of entities (usually atoms or molecules) in a substance is proportional to its physical mass.

Avogadro's number is a proportion that relates molar mass on an atomic scale to physical mass on a human scale. Avogadro's number is defined as the number of elementary particles (molecules, atoms, compounds, etc.) per mole of a substance. It is equal to $6.022 \times 10^{23}\ \text{mol}^{-1}$and is expressed as the symbol N_A.

Avogadro's number is a similar concept to that of a dozen or a gross. A dozen molecules is 12 molecules. A gross of molecules is 144 molecules. Avogadro's number is 6.022×10^{23}molecules. With Avogadro's number, scientists can discuss and compare very large numbers, which is useful because substances in everyday quantities contain very large numbers of atoms and molecules.

The Mole

The mole (abbreviated mol) is the SI measure of quantity of a "chemical entity," such as atoms, electrons, or protons. It is defined as the amount of a substance that contains as many particles as there are atoms in 12 grams of pure carbon-12. So, 1 mol contains 6.022×10^{23} elementary entities of the substance.

Chemical Computations with Avogadro's Number and the Mole

Avogadro's number is fundamental to understanding both the makeup of molecules and their interactions and combinations. For example, since one atom of oxygen will combine with two atoms of hydrogen to create one molecule of water (H_2O), one mole of oxygen (6.022×10^{23} of O atoms) will combine with two moles of hydrogen ($2 \times 6.022 \times 10^{23}$ of H atoms) to make one mole of H_2O.

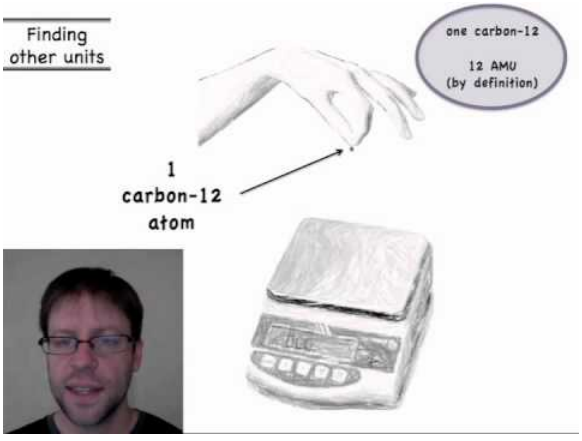
Another property of Avogadro's number is that the mass of one mole of a substance is equal to that substance's molecular weight. For example, the mean molecular weight of water is 18.015 atomic mass units (amu), so one mole of water weight 18.015 grams. This property simplifies many chemical computations.

If you have 1.25 grams of a molecule with molecular weight of 134.1 g/mol, how many moles of that molecule do you have?

$1.25g \times 1\ mole134.1g = 0.0093\ moles.1.25g \times 1\ mole134.1g = 0.0093\ moles.$

The Mole, Avogadro: This video introduces counting by mass, the mole, and how it relates to atomic mass units (AMU) and Avogadro's number.





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2.2.5: Average Atomic Mass

The average atomic mass of an element is the sum of the masses of its isotopes, each multiplied by its natural abundance.

Learning Objectives

- Calculate the average atomic mass of an element given its isotopes and their natural abundance

Key Points

- An element can have differing numbers of neutrons in its nucleus, but it always has the same number of protons. The versions of an element with different neutrons have different masses and are called isotopes.
- The average atomic mass for an element is calculated by summing the masses of the element's isotopes, each multiplied by its natural abundance on Earth.
- When doing any mass calculations involving elements or compounds, always use average atomic mass, which can be found on the periodic table.

Key Terms

- **mass number**: The total number of protons and neutrons in an atomic nucleus.
- **natural abundance**: The abundance of a particular isotope naturally found on the planet.
- **average atomic mass**: The mass calculated by summing the masses of an element's isotopes, each multiplied by its natural abundance on Earth.

The atomic number of an element defines the element's identity and signifies the number of protons in the nucleus of one atom. For example, the element hydrogen (the lightest element) will always have one proton in its nucleus. The element helium will always have two protons in its nucleus.

Isotopes

Atoms of the same element can, however, have differing numbers of neutrons in their nucleus. For example, stable helium atoms exist that contain either one or two neutrons, but both atoms have two protons. These different types of helium atoms have different masses (3 or 4 atomic mass units), and they are called isotopes. For any given isotope, the sum of the numbers of protons and neutrons in the nucleus is called the mass number. This is because each proton and each neutron weigh one atomic mass unit (amu). By adding together the number of protons and neutrons and multiplying by 1 amu, you can calculate the mass of the atom. All elements exist as a collection of isotopes. The word 'isotope' comes from the Greek 'isos' (meaning 'same') and 'topes' (meaning 'place') because the elements can occupy the same place on the periodic table while being different in subatomic construction.

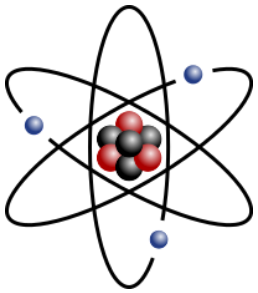

Figure: **Lithium Atom**: Stylized lithium-7 atom: 3 protons (red), 4 neutrons (black), and 3 electrons (blue). (Lithium also has another, rarer isotope with only 2 neutrons.)

Calculating Average Atomic Mass

The average atomic mass of an element is the sum of the masses of its isotopes, each multiplied by its natural abundance (the decimal associated with percent of atoms of that element that are of a given isotope).

Average atomic mass = $f_1M_1 + f_2M_2 + \ldots + f_nM_n$where f is the fraction representing the natural abundance of the isotope and M is the mass number (weight) of the isotope.

The average atomic mass of an element can be found on the periodic table, typically under the elemental symbol. When data are available regarding the natural abundance of various isotopes of an element, it is simple to calculate the average atomic mass.

- For helium, there is approximately one isotope of Helium-3 for every million isotopes of Helium-4; therefore, the average atomic mass is very close to 4 amu (4.002602 amu).
- Chlorine consists of two major isotopes, one with 18 neutrons (75.77 percent of natural chlorine atoms) and one with 20 neutrons (24.23 percent of natural chlorine atoms). The atomic number of chlorine is 17 (it has 17 protons in its nucleus).

To calculate the average mass, first convert the percentages into fractions (divide them by 100). Then, calculate the mass numbers. The chlorine isotope with 18 neutrons has an abundance of 0.7577 and a mass number of 35 amu. To calculate the average atomic mass, multiply the fraction by the mass number for each isotope, then add them together.

Average atomic mass of chlorine = (0.7577 ·· 35 amu) + (0.2423 ·· 37 amu) = 35.48 amu

Another example is to calculate the atomic mass of boron (B), which has two isotopes: B-10 with 19.9% natural abundance, and B-11 with 80.1% abundance. Therefore,

Average atomic mass of boron = (0.199··10 amu) + (0.801··11 amu) = 10.80 amu

Whenever we do mass calculations involving elements or compounds (combinations of elements), we always use average atomic masses.

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SECTION OVERVIEW

2.3: Chemical Reactions

Topic hierarchy

2.3.1: The Chemical Basis of Life

2.3.2: Energy Changes in Chemical Reactions

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2.3.1: The Chemical Basis of Life

Carbon is the most important element to living things because it can form many different kinds of bonds and form essential compounds.

Learning Objectives

- Explain the properties of carbon that allow it to serve as a building block for biomolecules

Key Points

- All living things contain carbon in some form.
- Carbon is the primary component of macromolecules, including proteins, lipids, nucleic acids, and carbohydrates.
- Carbon's molecular structure allows it to bond in many different ways and with many different elements.
- The carbon cycle shows how carbon moves through the living and non-living parts of the environment.

Key Terms

- **octet rule**: A rule stating that atoms lose, gain, or share electrons in order to have a full valence shell of 8 electrons (has some exceptions).
- **carbon cycle**: the physical cycle of carbon through the earth's biosphere, geosphere, hydrosphere, and atmosphere; includes such processes as photosynthesis, decomposition, respiration and carbonification
- **macromolecule**: a very large molecule, especially used in reference to large biological polymers (e.g., nucleic acids and proteins)

Carbon is the fourth most abundant element in the universe and is the building block of life on earth. On earth, carbon circulates through the land, ocean, and atmosphere, creating what is known as the Carbon Cycle. This global carbon cycle can be divided further into two separate cycles: the geological carbon cycles takes place over millions of years, whereas the biological or physical carbon cycle takes place from days to thousands of years. In a nonliving environment, carbon can exist as carbon dioxide (CO_2), carbonate rocks, coal, petroleum, natural gas, and dead organic matter. Plants and algae convert carbon dioxide to organic matter through the process of photosynthesis, the energy of light.



Figure: **Carbon is present in all life**: All living things contain carbon in some form, and carbon is the primary component of macromolecules, including proteins, lipids, nucleic acids, and carbohydrates. Carbon exists in many forms in this leaf, including in the cellulose to form the leaf's structure and in chlorophyll, the pigment which makes the leaf green.

Carbon is Important to Life

In its metabolism of food and respiration, an animal consumes glucose ($C_6H_{12}O_6$), which combines with oxygen (O_2) to produce carbon dioxide (CO_2), water (H_2O), and energy, which is given off as heat. The animal has no need for the carbon dioxide and releases it into the atmosphere. A plant, on the other hand, uses the opposite reaction of an animal through photosynthesis. It intakes carbon dioxide, water, and energy from sunlight to make its own glucose and oxygen gas. The glucose is used for chemical energy, which the plant metabolizes in a similar way to an animal. The plant then emits the remaining oxygen into the environment.

Cells are made of many complex molecules called macromolecules, which include proteins, nucleic acids (RNA and DNA), carbohydrates, and lipids. The macromolecules are a subset of organic molecules (any carbon-containing liquid, solid, or gas) that are especially important for life. The fundamental component for all of these macromolecules is carbon. The carbon atom has unique properties that allow it to form covalent bonds to as many as four different atoms, making this versatile element ideal to serve as the basic structural component, or "backbone," of the macromolecules.

Structure of Carbon

Individual carbon atoms have an incomplete outermost electron shell. With an atomic number of 6 (six electrons and six protons), the first two electrons fill the inner shell, leaving four in the second shell. Therefore, carbon atoms can form four covalent bonds with other atoms to satisfy the octet rule. The methane molecule provides an example: it has the chemical formula CH_4. Each of its four hydrogen atoms forms a single covalent bond with the carbon atom by sharing a pair of electrons. This results in a filled outermost shell.

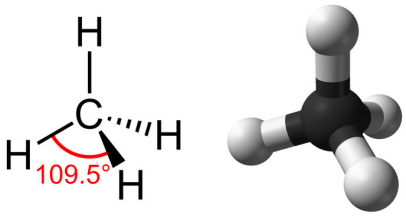

Figure: **Structure of Methane**: Methane has a tetrahedral geometry, with each of the four hydrogen atoms spaced 109.5° apart.

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2.3.2: Energy Changes in Chemical Reactions

Chemical reactions often produce changes in energy.

Learning Objectives

- Describe the types of energy changes that can occur in chemical reactions

Key Points

- Chemical reactions often involve changes in energy due to the breaking and formation of bonds.
- Reactions in which energy is released are exothermic reactions, while those that take in heat energy are endothermic.

Key Terms

- **endothermic**: A description of a chemical reaction that absorbs heat energy from its surroundings.
- **enthalpy**: In thermodynamics, a measure of the heat content of a chemical or physical system. The change in enthalpy of a chemical reaction is symbolized as ΔH.
- **exothermic**: A description of a chemical reaction that releases heat energy to its surroundings.

Due to the absorption of energy when chemical bonds are broken, and the release of energy when chemical bonds are formed, chemical reactions almost always involve a change in energy between products and reactants. By the Law of Conservation of Energy, however, we know that the total energy of a system must remain unchanged, and that oftentimes a chemical reaction will absorb or release energy in the form of heat, light, or both. The energy change in a chemical reaction is due to the difference in the amounts of stored chemical energy between the products and the reactants. This stored chemical energy, or heat content, of the system is known as its enthalpy.

Exothermic Reactions

Exothermic reactions release heat and light into their surroundings. For example, combustion reactions are usually exothermic. In exothermic reactions, the products have less enthalpy than the reactants, and as a result, an exothermic reaction is said to have a *negative* enthalpy of reaction. This means that the energy required to break the bonds in the reactants is less than the energy released when new bonds form in the products. Excess energy from the reaction is released as heat and light.



Figure: **Chemical reaction**: A thermite reaction, which produces molten iron.

Endothermic Reactions

Endothermic reactions, on the other hand, absorb heat and/or light from their surroundings. For example, decomposition reactions are usually endothermic. In endothermic reactions, the products have more enthalpy than the reactants. Thus, an endothermic reaction is said to have a *positive* enthalpy of reaction. This means that the energy required to break the bonds in the reactants is more than the energy released when new bonds form in the products; in other words, the reaction requires energy to proceed.

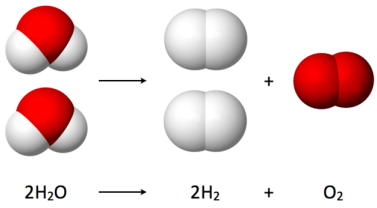

Figure: **The decomposition of water into hydrogen and oxygen**: When water is heated to over 2000 degrees Celsius, a small fraction will decompose into hydrogen and oxygen. Significant heat energy is needed for this reaction to proceed, so the reaction is endothermic.

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SECTION OVERVIEW

2.4: Inorganic Compounds

Topic hierarchy

2.4.1: Water's State: Gas, Liquid, and Solid

2.4.2: pH, Buffers, Acids, and Bases

2.4.3: Overview of the Acid- Base Properties of Salt

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2.4.1: Water's State: Gas, Liquid, and Solid

The orientation of hydrogen bonds as water changes states dictates the properties of water in its gaseous, liquid, and solid forms.

Learning Objectives

- Explain the biological significance of ice's ability to float on water

Key Points

- As water is boiled, kinetic energy causes the hydrogen bonds to break completely and allows water molecules to escape into the air as gas (steam or water vapor).
- When water freezes, water molecules form a crystalline structure maintained by hydrogen bonding.
- Solid water, or ice, is less dense than liquid water.
- Ice is less dense than water because the orientation of hydrogen bonds causes molecules to push farther apart, which lowers the density.
- For other liquids, solidification when the temperature drops includes the lowering of kinetic energy, which allows molecules to pack more tightly and makes the solid denser than its liquid form.
- Because ice is less dense than water, it is able to float at the surface of water.

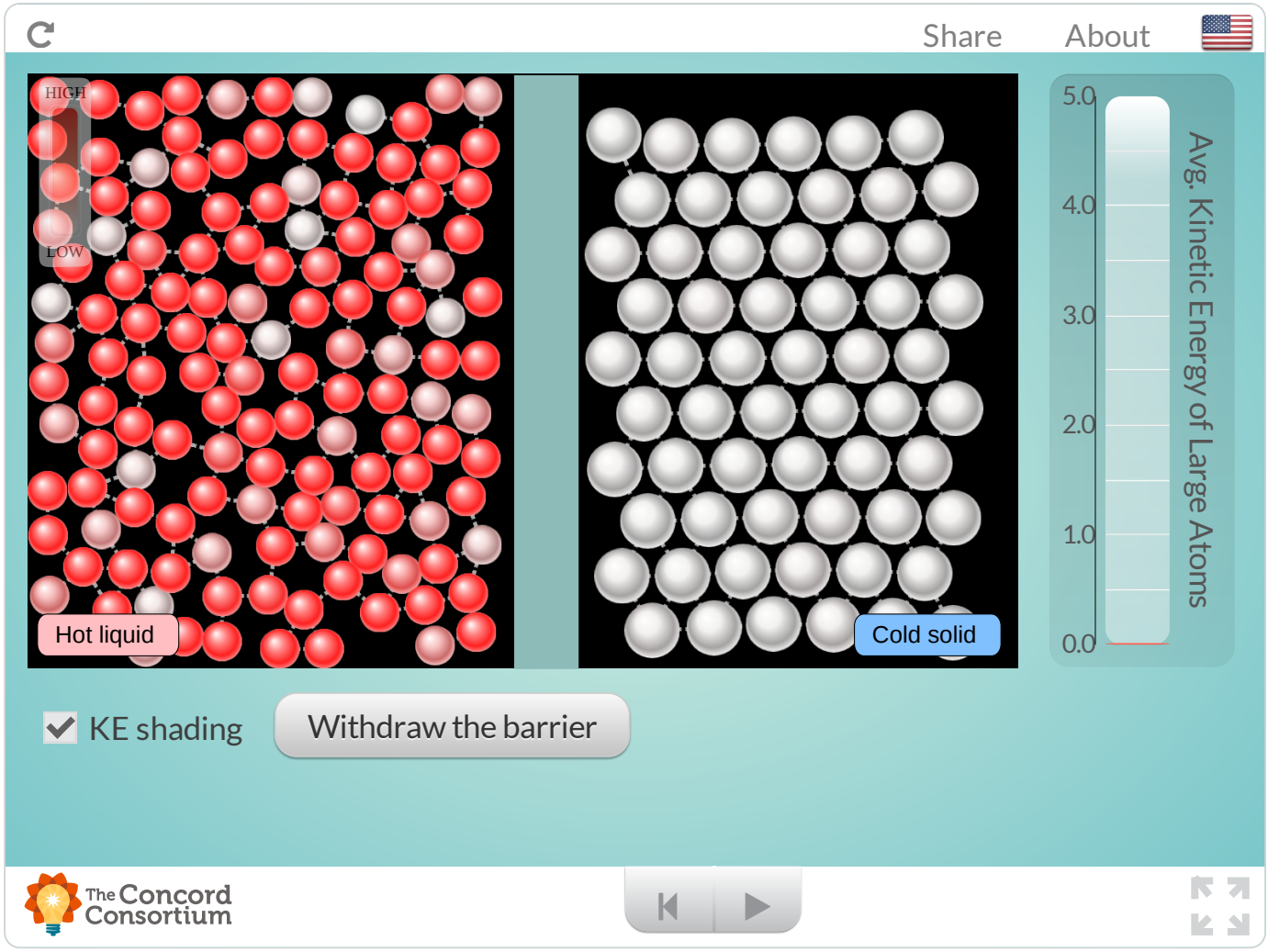
Key Terms

- **density**: A measure of the amount of matter contained by a given volume.

Water's States: Gas, Liquid, and Solid

The formation of hydrogen bonds is an important quality of liquid water that is crucial to life as we know it. As water molecules make hydrogen bonds with each other, water takes on some unique chemical characteristics compared to other liquids, and since living things have a high water content, understanding these chemical features is key to understanding life. In liquid water, hydrogen bonds are constantly formed and broken as the water molecules slide past each other. The breaking of these bonds is caused by the motion (kinetic energy) of the water molecules due to the heat contained in the system. When the heat is raised as water is boiled, the higher kinetic energy of the water molecules causes the hydrogen bonds to break completely and allows water molecules to escape into the air as gas (steam or water vapor). On the other hand, when the temperature of water is reduced and water freezes, the water molecules form a crystalline structure maintained by hydrogen bonding (there is not enough energy to break the hydrogen bonds). This makes ice less dense than liquid water, a phenomenon not seen in the solidification of other liquids.

Phases of matter: See what happens to intermolecular bonds during phase changes in this interactive.



Water's lower density in its solid form is due to the way hydrogen bonds are oriented as it freezes: the water molecules are pushed farther apart compared to liquid water. With most other liquids, solidification when the temperature drops includes the lowering of kinetic energy between molecules, allowing them to pack even more tightly than in liquid form and giving the solid a greater density than the liquid.

The low density of ice, an anomaly, causes it to float at the surface of liquid water, such as an iceberg or the ice cubes in a glass of water. In lakes and ponds, ice forms on the surface of the water creating an insulating barrier that protects the animals and plant life in the pond from freezing. Without this layer of insulating ice, plants and animals living in the pond would freeze in the solid block of ice and could not survive. The detrimental effect of freezing on living organisms is caused by the expansion of ice relative to liquid water. The ice crystals that form upon freezing rupture the delicate membranes essential for the function of living cells, irreversibly damaging them. Cells can only survive freezing if the water in them is temporarily replaced by another liquid like glycerol.

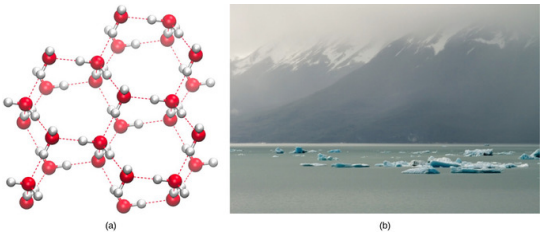


Figure: **Ice Density**: Hydrogen bonding makes ice less dense than liquid water. The (a) lattice structure of ice makes it less dense than the freely flowing molecules of liquid water, enabling it to (b) float on water.

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2.4.2: pH, Buffers, Acids, and Bases

Acids dissociate into H^+ and lower pH, while bases dissociate into OH^- and raise pH; buffers can absorb these excess ions to maintain pH.

Learning Objectives

- Explain the composition of buffer solutions and how they maintain a steady pH

Key Points

- A basic solution will have a pH above 7.0, while an acidic solution will have a pH below 7.0.
- Buffers are solutions that contain a weak acid and its a conjugate base; as such, they can absorb excess H^+ ions or OH^- ions, thereby maintaining an overall steady pH in the solution.
- pH is equal to the negative logarithm of the concentration of H^+ ions in solution: $pH = – \log[H^+]$.

Key Terms

- **alkaline**: having a pH greater than 7; basic
- **acidic**: having a pH less than 7
- **buffer**: a solution composed of a weak acid and its conjugate base that can be used to stabilize the pH of a solution

Self-Ionization of Water

Hydrogen ions are spontaneously generated in pure water by the dissociation (ionization) of a small percentage of water molecules into equal numbers of hydrogen (H^+) ions and hydroxide (OH^-) ions. The hydroxide ions remain in solution because of their hydrogen bonds with other water molecules; the hydrogen ions, consisting of naked protons, are immediately attracted to un-ionized water molecules and form hydronium ions (H_30^+). By convention, scientists refer to hydrogen ions and their concentration as if they were free in this state in liquid water.

$2H2O \leftrightharpoons H3O^+ + OH^- 2H2O \leftrightharpoons H3O^+ + OH^-$

The concentration of hydrogen ions dissociating from pure water is 1×10^{-7} moles H^+ ions per liter of water. The pH is calculated as the negative of the base 10 logarithm of this concentration:

$pH = -\log[H^+]$

The negative log of 1×10^{-7} is equal to 7.0, which is also known as neutral pH. Human cells and blood each maintain near-neutral pH.

pH Scale

The pH of a solution indicates its acidity or basicity (alkalinity). The pH scale is an inverse logarithm that ranges from 0 to 14: anything below 7.0 (ranging from 0.0 to 6.9) is acidic, and anything above 7.0 (from 7.1 to 14.0) is basic (or alkaline). Extremes in pH in either direction from 7.0 are usually considered inhospitable to life. The pH in cells (6.8) and the blood (7.4) are both very close to neutral, whereas the environment in the stomach is highly acidic, with a pH of 1 to 2.

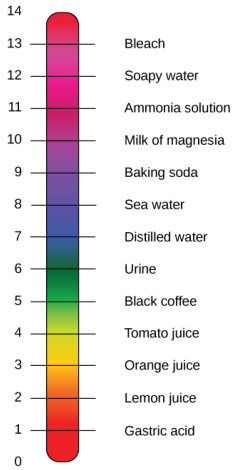

Figure: **The pH scale**: The pH scale measures the concentration of hydrogen ions (H^+) in a solution.

Non-neutral pH readings result from dissolving acids or bases in water. Using the negative logarithm to generate positive integers, high concentrations of hydrogen ions yield a low pH, and low concentrations a high pH.

An acid is a substance that increases the concentration of hydrogen ions (H^+) in a solution, usually by dissociating one of its hydrogen atoms. A base provides either hydroxide ions (OH^-) or other negatively-charged ions that react with hydrogen ions in solution, thereby reducing the concentration of H^+ and raising the pH.

Strong Acids and Strong Bases

The stronger the acid, the more readily it donates H^+. For example, hydrochloric acid (HCl) is highly acidic and completely dissociates into hydrogen and chloride ions, whereas the acids in tomato juice or vinegar do not completely dissociate and are considered weak acids; conversely, strong bases readily donate OH^- and/or react with hydrogen ions. Sodium hydroxide (NaOH) and many household cleaners are highly basic and give up OH^- rapidly when placed in water; the OH^- ions react with H^+ in solution, creating new water molecules and lowering the amount of free H^+ in the system, thereby raising the overall pH. An example of a weak basic solution is seawater, which has a pH near 8.0, close enough to neutral that well-adapted marine organisms thrive in this alkaline environment.

Buffers

How can organisms whose bodies require a near-neutral pH ingest acidic and basic substances (a human drinking orange juice, for example) and survive? Buffers are the key. Buffers usually consist of a weak acid and its conjugate base; this enables them to readily absorb excess H^+ or OH^-, keeping the system's pH within a narrow range.

Maintaining a constant blood pH is critical to a person's well-being. The buffer that maintains the pH of human blood involves carbonic acid (H_2CO_3), bicarbonate ion (HCO_3^-), and carbon dioxide (CO_2). When bicarbonate ions combine with free hydrogen ions and become carbonic acid, hydrogen ions are removed, moderating pH changes. Similarly, excess carbonic acid can be converted into carbon dioxide gas and exhaled through the lungs; this prevents too many free hydrogen ions from building up in the blood and dangerously reducing its pH; likewise, if too much OH^- is introduced into the system, carbonic acid will combine with it to create bicarbonate, lowering the pH. Without this buffer system, the body's pH would fluctuate enough to jeopardize survival.

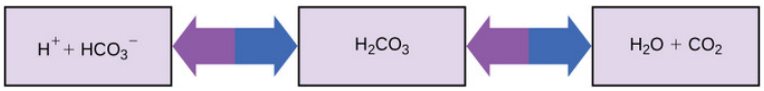

Figure: **Buffers in the body**: This diagram shows the body's buffering of blood pH levels: the blue arrows show the process of raising pH as more CO2 is made; the purple arrows indicate the reverse process, lowering pH as more bicarbonate is created.

Antacids, which combat excess stomach acid, are another example of buffers. Many over-the-counter medications work similarly to blood buffers, often with at least one ion (usually carbonate) capable of absorbing hydrogen and moderating pH, bringing relief to those that suffer "heartburn" from stomach acid after eating.

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2.4.3: Overview of the Acid- Base Properties of Salt

Some salts, such as ammonium bicarbonate (NH_4HCO_3), contain cations and anions that can both undergo hydrolysis.

Learning Objectives

- Predict the pH of a solution of a salt containing cations and anions, both of which participate in hydrolysis.

Key Points

- Basic salts result from the neutralization of a strong base with a weak acid.
- Acid salts result from the neutralization of a strong acid with a weak base.
- For salts in which both cation and anion are capable of hydrolysis, compare K_a and K_b values to determine the solution ‘s resulting pH.

Key Terms

- **neutralization reaction**: a reaction between an acid and a base in which water and a salt are formed
- **hydrolysis**: a reaction with water in which chemical bonds break
- **salt**: in acid-base chemistry, one of the products in a neutralization reaction

Summary of Acidic and Basic Salts

As we have discussed, salts can form acidic or basic solutions if their cations and/or anions are hydrolyzable (able to react in water). Basic salts form from the neutralization of a strong base and a weak acid; for instance, the reaction of sodium hydroxide (a strong base) with acetic acid (a weak acid) will yield water and sodium acetate. Sodium acetate is a basic salt; the acetate ion is capable of deprotonating water, thereby raising the solution’s pH.

Acid salts are the converse of basic salts; they are formed in the neutralization reaction between a strong acid and a weak base. The conjugate acid of the weak base makes the salt acidic. For instance, in the reaction of hydrochloric acid (a strong acid) with ammonia (a weak base), water is formed, along with ammonium chloride. The ammonium ion contains a hydrolyzable proton, which makes it an acid salt.

Salts in Which Both Ions Hydrolyze

The following is a more complicated scenario in which a salt contains a cation and an anion, both of which are capable of participating in hydrolysis. A good example of such a salt is ammonium bicarbonate, NH_4HCO_3; like all ammonium salts, it is highly soluble, and its dissociation reaction in water is as follows:

$$NH4CO3(s)→NH+4(aq)+HCO−3(aq)NH4CO3(s)→NH4+(aq)+HCO3−(aq)$$

However, as we have already discussed, the ammonium ion acts as a weak acid in solution, while the bicarbonate ion acts as a weak base. The reactions are as follows:

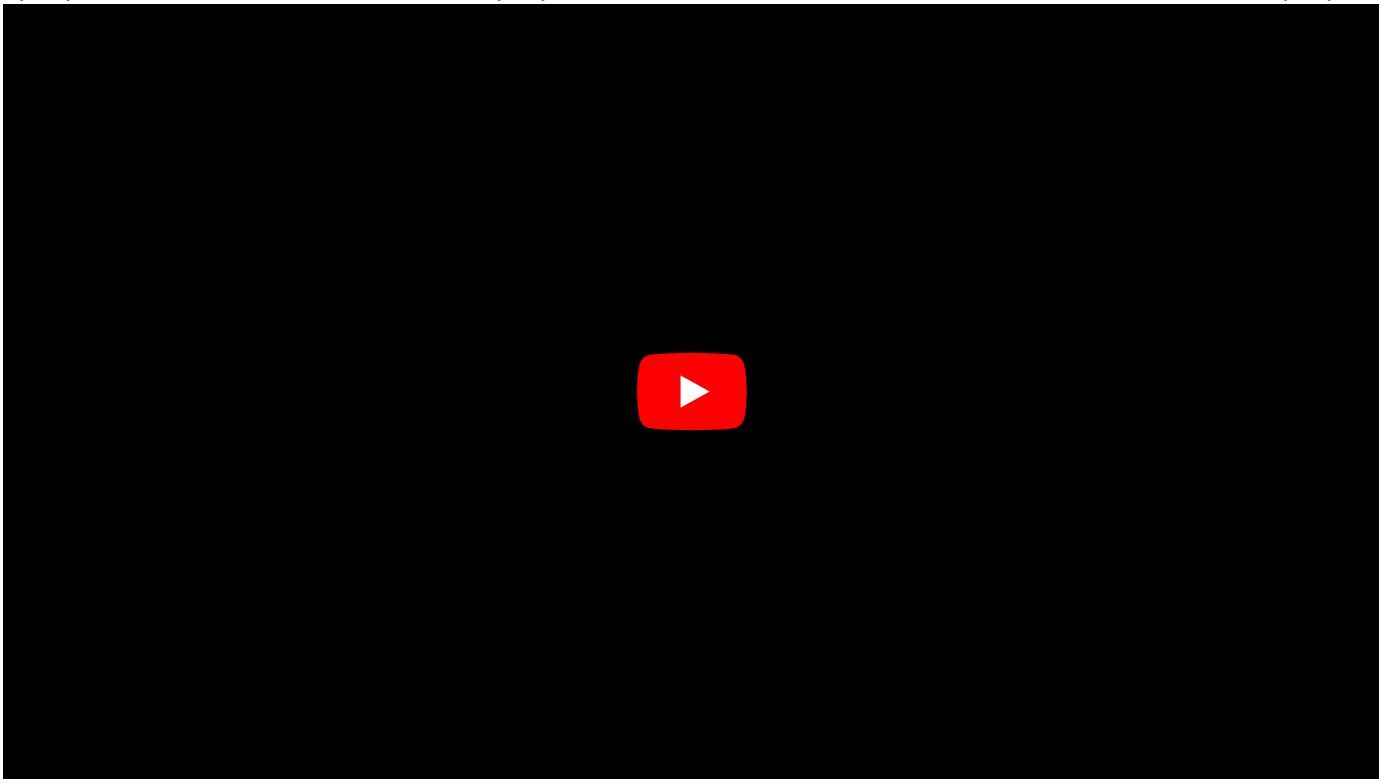
$$NH+4(aq)+H2O(l)⇌H3O+(aq)+NH3(aq)Ka=5.6×10−10NH4+(aq)+H2O(l)⇌H3O+(aq)+NH3(aq)Ka=5.6×10−10$$

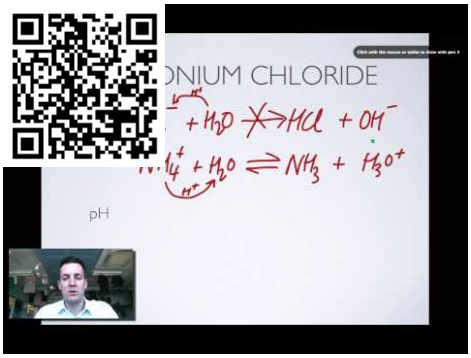
$$HCO−3(aq)+H2O(l)⇌H2CO3(aq)+OH−(aq)Kb=2.4×10−8HCO3−(aq)+H2O(l)⇌H2CO3(aq)+OH−(aq)Kb=2.4×10−8$$

Because both ions can hydrolyze, will a solution of ammonium bicarbonate be acidic or basic? We can determine the answer by comparing K_a and K_b values for each ion. In this case, the value of K_b for bicarbonate is greater than the value of K_a for ammonium. Therefore, bicarbonate is a slightly more alkaline than ammonium is acidic, and a solution of ammonium bicarbonate in pure water will be slightly basic (pH > 7.0). In summary, when a salt contains two ions that hydrolyze, compare their K_a and K_b values:

- If $K_a > K_b$, the solution will be slightly acidic.
- If $K_b > K_a$, the solution will be slightly basic.

Hydrolysis of salts: This video examines the hydrolysis of an acid salt, a basic salt, and a salt in which both ions hydrolyze.





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SECTION OVERVIEW

2.5: Organic Compounds

Topic hierarchy

2.5.1: Carbohydrate Molecules

2.5.2: Lipid Molecules

2.5.3: DNA and RNA

2.5.4: Amino Acids

2.5.5: Types and Functions of Protiens

2.5.6: ATP: Adenosine Triphosphate

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2.5.1: Carbohydrate Molecules

Carbohydrates are essential macromolecules that are classified into three subtypes: monosaccharides, disaccharides, and polysaccharides.

Learning Objectives

- Describe the structure of mono-, di-, and poly-saccharides

Key Points

- Monosaccharides are simple sugars made up of three to seven carbons, and they can exist as a linear chain or as ring-shaped molecules.
- Glucose, galactose, and fructose are monosaccharide isomers, which means they all have the same chemical formula but differ structurally and chemically.
- Disaccharides form when two monosaccharides undergo a dehydration reaction (a condensation reaction); they are held together by a covalent bond.
- Sucrose (table sugar) is the most common disaccharide, which is composed of the monomers glucose and fructose.
- A polysaccharide is a long chain of monosaccharides linked by glycosidic bonds; the chain may be branched or unbranched and can contain many types of monosaccharides.

Key Terms

- **isomer**: Any of two or more compounds with the same molecular formula but with different structure.
- **dehydration reaction**: A chemical reaction in which two molecules are covalently linked in a reaction that generates H2O as a second product.
- **biopolymer**: Any macromolecule of a living organism that is formed from the polymerization of smaller entities; a polymer that occurs in a living organism or results from life.

Carbohydrates can be represented by the stoichiometric formula $(CH_2O)_n$, where n is the number of carbons in the molecule. Therefore, the ratio of carbon to hydrogen to oxygen is 1:2:1 in carbohydrate molecules. The origin of the term “carbohydrate” is based on its components: carbon (“carbo”) and water (“hydrate”). Carbohydrates are classified into three subtypes: monosaccharides, disaccharides, and polysaccharides.

Monosaccharides

Monosaccharides (mono- = “one”; sacchar- = “sweet”) are simple sugars. In monosaccharides, the number of carbons usually ranges from three to seven. If the sugar has an aldehyde group (the functional group with the structure R-CHO), it is known as an aldose, and if it has a ketone group (the functional group with the structure RC(=O)R’), it is known as a ketose. Depending on the number of carbons in the sugar, they also may be known as trioses (three carbons), pentoses (five carbons), and or hexoses (six carbons). Monosaccharides can exist as a linear chain or as ring-shaped molecules; in aqueous solutions they are usually found in ring forms.

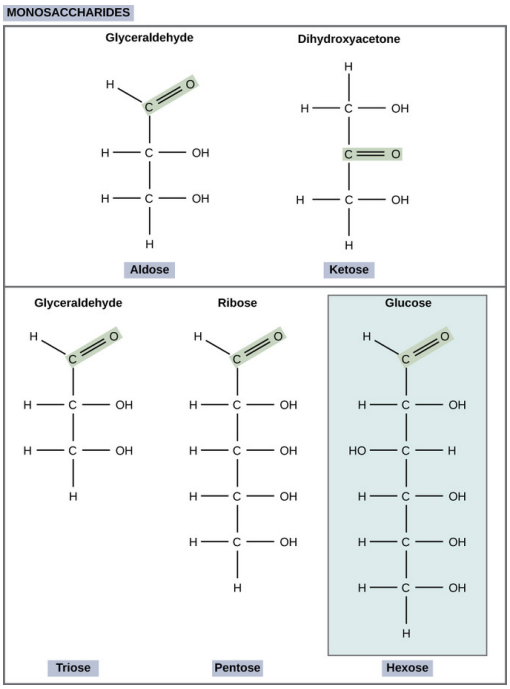

Figure: **Monosaccharides**: Monosaccharides are classified based on the position of their carbonyl group and the number of carbons in the backbone. Aldoses have a carbonyl group (indicated in green) at the end of the carbon chain, and ketoses have a carbonyl group in the middle of the carbon chain. Trioses, pentoses, and hexoses have three, five, and six carbon backbones, respectively.

Common Monosaccharides

Glucose ($C_6H_{12}O_6$) is a common monosaccharide and an important source of energy. During cellular respiration, energy is released from glucose and that energy is used to help make adenosine triphosphate (ATP). Plants synthesize glucose using carbon dioxide and water, and glucose, in turn, is used for energy requirements for the plant.

Galactose (a milk sugar) and fructose (found in fruit) are other common monosaccharides. Although glucose, galactose, and fructose all have the same chemical formula ($C_6H_{12}O_6$), they differ structurally and stereochemically. This makes them different molecules despite sharing the same atoms in the same proportions, and they are all isomers of one another, or isomeric monosaccharides. Glucose and galactose are aldoses, and fructose is a ketose.

Disaccharides

Disaccharides (di- = “two”) form when two monosaccharides undergo a dehydration reaction (also known as a condensation reaction or dehydration synthesis). During this process, the hydroxyl group of one monosaccharide combines with the hydrogen of another monosaccharide, releasing a molecule of water and forming a covalent bond. A covalent bond formed between a carbohydrate molecule and another molecule (in this case, between two monosaccharides) is known as a glycosidic bond. Glycosidic bonds (also called glycosidic linkages) can be of the alpha or the beta type.

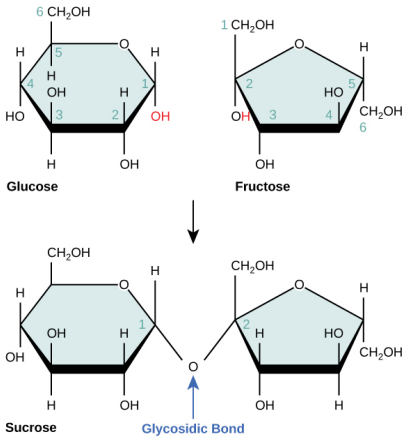

Figure: **Disaccharides**: Sucrose is formed when a monomer of glucose and a monomer of fructose are joined in a dehydration reaction to form a glycosidic bond. In the process, a water molecule is lost. By convention, the carbon atoms in a monosaccharide are numbered from the terminal carbon closest to the carbonyl group. In sucrose, a glycosidic linkage is formed between carbon 1 in glucose and carbon 2 in fructose.

Common Disaccharides

Common disaccharides include lactose, maltose, and sucrose. Lactose is a disaccharide consisting of the monomers glucose and galactose. It is found naturally in milk. Maltose, or malt sugar, is a disaccharide formed by a dehydration reaction between two glucose molecules. The most common disaccharide is sucrose, or table sugar, which is composed of the monomers glucose and fructose.

Polysaccharides

A long chain of monosaccharides linked by glycosidic bonds is known as a polysaccharide (poly- = “many”). The chain may be branched or unbranched, and it may contain different types of monosaccharides. Starch, glycogen, cellulose, and chitin are primary examples of polysaccharides.

Plants are able to synthesize glucose, and the excess glucose is stored as starch in different plant parts, including roots and seeds. Starch is the stored form of sugars in plants and is made up of glucose monomers that are joined by α1-4 or 1-6 glycosidic bonds. The starch in the seeds provides food for the embryo as it germinates while the starch that is consumed by humans is broken down by enzymes into smaller molecules, such as maltose and glucose. The cells can then absorb the glucose.

Common Polysaccharides

Glycogen is the storage form of glucose in humans and other vertebrates. It is made up of monomers of glucose. Glycogen is the animal equivalent of starch and is a highly branched molecule usually stored in liver and muscle cells. Whenever blood glucose levels decrease, glycogen is broken down to release glucose in a process known as glycogenolysis.

Cellulose is the most abundant natural biopolymer. The cell wall of plants is mostly made of cellulose and provides structural support to the cell. Cellulose is made up of glucose monomers that are linked by β 1-4 glycosidic bonds. Every other glucose monomer in cellulose is flipped over, and the monomers are packed tightly as extended long chains. This gives cellulose its rigidity and high tensile strength—which is so important to plant cells.

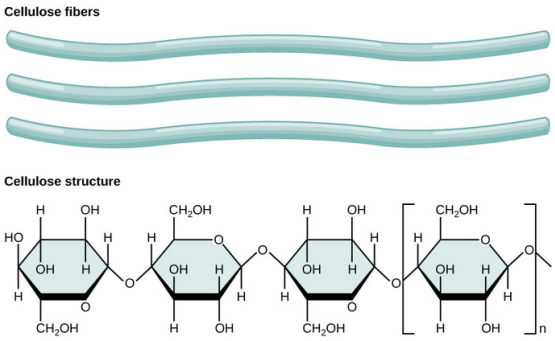

Figure: **Polysaccharides**: In cellulose, glucose monomers are linked in unbranched chains by β 1-4 glycosidic linkages. Because of the way the glucose subunits are joined, every glucose monomer is flipped relative to the next one resulting in a linear, fibrous structure.

Carbohydrate Function

Carbohydrates serve various functions in different animals. Arthropods have an outer skeleton, the exoskeleton, which protects their internal body parts. This exoskeleton is made of chitin, which is a polysaccharide-containing nitrogen. It is made of repeating units of N-acetyl-β-d-glucosamine, a modified sugar. Chitin is also a major component of fungal cell walls

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2.5.2: Lipid Molecules

Fats and oils, which may be saturated or unsaturated, can be unhealthy but also serve important functions for plants and animals.

Learning Objectives

- Differentiate between saturated and unsaturated fatty acids

Key Points

- Fats provide energy, insulation, and storage of fatty acids for many organisms.
- Fats may be saturated (having single bonds) or unsaturated (having double bonds).
- Unsaturated fats may be cis (hydrogens in same plane) or trans (hydrogens in two different planes).
- Olive oil, a monounsaturated fat, has a single double bond whereas canola oil, a polyunsaturated fat, has more than one double bond.
- Omega-3 fatty acid and omega-6 fatty acid are essential for human biological processes, but they must be ingested in the diet because they cannot be synthesized.

Key Terms

- **hydrogenation**: The chemical reaction of hydrogen with another substance, especially with an unsaturated organic compound, and usually under the influence of temperature, pressure and catalysts.
- **ester**: Compound most often formed by the condensation of an alcohol and an acid, by removing water. It contains the functional group carbon-oxygen double bond joined via carbon to another oxygen atom.
- **carboxyl**: A univalent functional group consisting of a carbonyl and a hydroxyl functional group (-CO.OH); characteristic of carboxylic acids.

Fats have important functions, and many vitamins are fat soluble. Fats serve as a long-term storage form of fatty acids and act as a source of energy. They also provide insulation for the body.

Glycerol and Fatty Acids

A fat molecule consists of two main components: glycerol and fatty acids. Glycerol is an alcohol with three carbons, five hydrogens, and three hydroxyl (OH) groups. Fatty acids have a long chain of hydrocarbons with a carboxyl group attached and may have 4-36 carbons; however, most of them have 12-18. In a fat molecule, the fatty acids are attached to each of the three carbons of the glycerol molecule with an ester bond through the oxygen atom. During the ester bond formation, three molecules are released. Since fats consist of three fatty acids and a glycerol, they are also called triacylglycerols or triglycerides.

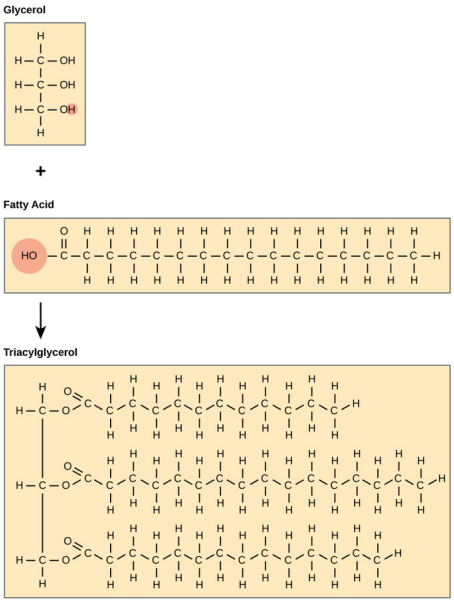

Figure: **Triacylglycerols**: Triacylglycerol is formed by the joining of three fatty acids to a glycerol backbone in a dehydration reaction. Three molecules of water are released in the process.

Saturated vs. Unsaturated Fatty Acids

Fatty acids may be saturated or unsaturated. In a fatty acid chain, if there are only single bonds between neighboring carbons in the hydrocarbon chain, the fatty acid is said to be saturated. Saturated fatty acids are saturated with hydrogen since single bonds increase the number of hydrogens on each carbon. Stearic acid and palmitic acid, which are commonly found in meat, are examples of saturated fats.

When the hydrocarbon chain contains a double bond, the fatty acid is said to be unsaturated. Oleic acid is an example of an unsaturated fatty acid. Most unsaturated fats are liquid at room temperature and are called oils. If there is only one double bond in the molecule, then it is known as a monounsaturated fat; e.g. olive oil. If there is more than one double bond, then it is known as a polyunsaturated fat; e.g. canola oil. Unsaturated fats help to lower blood cholesterol levels whereas saturated fats contribute to plaque formation in the arteries.

Unsaturated fats or oils are usually of plant origin and contain cis unsaturated fatty acids. Cis and trans indicate the configuration of the molecule around the double bond. If hydrogens are present in the same plane, it is referred to as a cis fat; if the hydrogen atoms are on two different planes, it is referred to as a trans fat. The cis double bond causes a bend or a “kink” that prevents the fatty acids from packing tightly, keeping them liquid at room temperature.

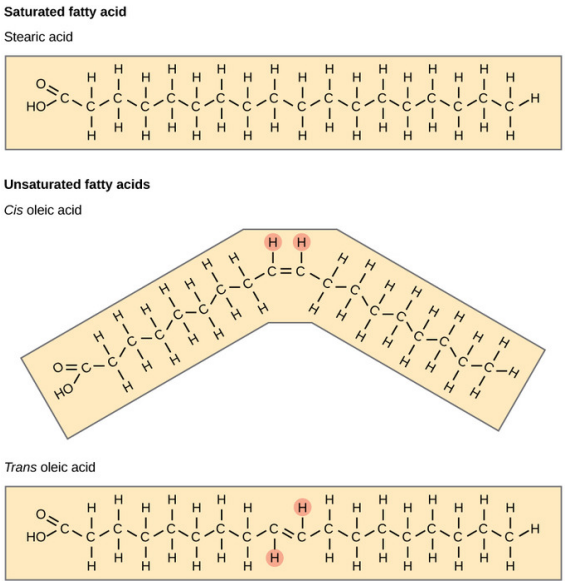

Figure: **Fatty Acids**: Saturated fatty acids have hydrocarbon chains connected by single bonds only. Unsaturated fatty acids have one or more double bonds. Each double bond may be in a cis or trans configuration. In the cis configuration, both hydrogens are on the same side of the hydrocarbon chain. In the trans configuration, the hydrogens are on opposite sides. A cis double bond causes a kink in the chain.

Trans Fats

In the food industry, oils are artificially hydrogenated to make them semi-solid and of a consistency desirable for many processed food products. During this hydrogenation process, gas is bubbled through oils to solidify them, and the double bonds of the cis-conformation in the hydrocarbon chain may be converted to double bonds in the trans-conformation.

Margarine, some types of peanut butter, and shortening are examples of artificially-hydrogenated trans fats. Recent studies have shown that an increase in trans fats in the human diet may lead to an increase in levels of low-density lipoproteins (LDL), or “bad” cholesterol, which in turn may lead to plaque deposition in the arteries, resulting in heart disease. Many fast food restaurants have recently banned the use of trans fats, and food labels are required to display the trans fat content.

Essential Fatty Acids

Essential fatty acids are fatty acids required for biological processes, but not synthesized by the human body. Consequently, they have to be supplemented through ingestion via the diet and are nutritionally very important. Omega-3 fatty acid, or alpha-linoleic acid (ALA), falls into this category and is one of only two fatty acids known to be essential for humans (the other being omega-6 fatty acid, or linoleic acid). These polyunsaturated fatty acids are called omega-3 because the third carbon from the end of the hydrocarbon chain is connected to its neighboring carbon by a double bond. Salmon, trout, and tuna are good sources of omega-3 fatty acids.

Research indicates that omega-3 fatty acids reduce the risk of sudden death from heart attacks, reduce triglycerides in the blood, lower blood pressure, and prevent thrombosis by inhibiting blood clotting. They also reduce inflammation and may help reduce the risk of some cancers in animals.

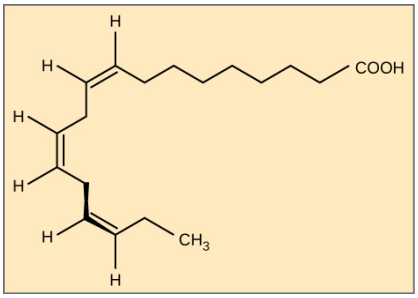

Figure: **Omega Fatty Acids**: Alpha-linolenic acid is an example of an omega-3 fatty acid. It has three cis double bonds and, as a result, a curved shape. For clarity, the carbons are not shown. Each singly bonded carbon has two hydrogens associated with it, also not shown.

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2.5.3: DNA and RNA

DNA and RNA are nucleic acids that carry out cellular processes, especially the regulation and expression of genes.

Learning Objectives

- Describe the structure of nucleic acids and the types of molecules that contain them

Key Points

- The two main types of nucleic acids are DNA and RNA.
- Both DNA and RNA are made from nucleotides, each containing a five-carbon sugar backbone, a phosphate group, and a nitrogen base.
- DNA provides the code for the cell ‘s activities, while RNA converts that code into proteins to carry out cellular functions.
- The sequence of nitrogen bases (A, T, C, G) in DNA is what forms an organism’s traits.
- The nitrogen bases A and T (or U in RNA) always go together and C and G always go together, forming the 5′-3′ phosphodiester linkage found in the nucleic acid molecules.

Key Terms

- **nucleotide**: the monomer comprising DNA or RNA molecules; consists of a nitrogenous heterocyclic base that can be a purine or pyrimidine, a five-carbon pentose sugar, and a phosphate group
- **genome**: the cell’s complete genetic information packaged as a double-stranded DNA molecule
- **monomer**: A relatively small molecule which can be covalently bonded to other monomers to form a polymer.

Types of Nucleic Acids

The two main types of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the genetic material found in all living organisms, ranging from single-celled bacteria to multicellular mammals. It is found in the nucleus of eukaryotes and in the chloroplasts and mitochondria. In prokaryotes, the DNA is not enclosed in a membranous envelope, but rather free-floating within the cytoplasm.

The entire genetic content of a cell is known as its genome and the study of genomes is genomics. In eukaryotic cells, but not in prokaryotes, DNA forms a complex with histone proteins to form chromatin, the substance of eukaryotic chromosomes. A chromosome may contain tens of thousands of genes. Many genes contain the information to make protein products; other genes code for RNA products. DNA controls all of the cellular activities by turning the genes “on” or “off. ”

The other type of nucleic acid, RNA, is mostly involved in protein synthesis. In eukaryotes, the DNA molecules never leave the nucleus but instead use an intermediary to communicate with the rest of the cell. This intermediary is the messenger RNA (mRNA). Other types of RNA—like rRNA, tRNA, and microRNA—are involved in protein synthesis and its regulation.

Nucleotides

DNA and RNA are made up of monomers known as nucleotides. The nucleotides combine with each other to form a polynucleotide: DNA or RNA. Each nucleotide is made up of three components:

1. a nitrogenous base
2. a pentose (five-carbon) sugar
3. a phosphate group

Each nitrogenous base in a nucleotide is attached to a sugar molecule, which is attached to one or more phosphate groups.

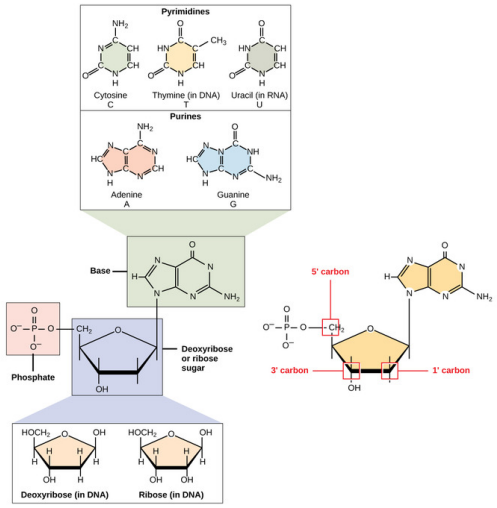

Figure: **DNA and RNA**: A nucleotide is made up of three components: a nitrogenous base, a pentose sugar, and one or more phosphate groups. Carbon residues in the pentose are numbered 1′ through 5′ (the prime distinguishes these residues from those in the base, which are numbered without using a prime notation). The base is attached to the 1′ position of the ribose, and the phosphate is attached to the 5′ position. When a polynucleotide is formed, the 5′ phosphate of the incoming nucleotide attaches to the 3′ hydroxyl group at the end of the growing chain. Two types of pentose are found in nucleotides, deoxyribose (found in DNA) and ribose (found in RNA). Deoxyribose is similar in structure to ribose, but it has an H instead of an OH at the 2′ position. Bases can be divided into two categories: purines and pyrimidines. Purines have a double ring structure, and pyrimidines have a single ring.

Nitrogenous Base

The nitrogenous bases are organic molecules and are so named because they contain carbon and nitrogen. They are bases because they contain an amino group that has the potential of binding an extra hydrogen, and thus, decreasing the hydrogen ion concentration in its environment, making it more basic. Each nucleotide in DNA contains one of four possible nitrogenous bases: adenine (A), guanine (G) cytosine (C), and thymine (T).

Adenine and guanine are classified as purines. The primary structure of a purine consists of two carbon-nitrogen rings. Cytosine, thymine, and uracil are classified as pyrimidines which have a single carbon-nitrogen ring as their primary structure. Each of these basic carbon-nitrogen rings has different functional groups attached to it. In molecular biology shorthand, the nitrogenous bases are simply known by their symbols A, T, G, C, and U. DNA contains A, T, G, and C whereas RNA contains A, U, G, and C.

Five-Carbon Sugar

The pentose sugar in DNA is deoxyribose and in RNA it is ribose. The difference between the sugars is the presence of the hydroxyl group on the second carbon of the ribose and hydrogen on the second carbon of the deoxyribose. The carbon atoms of the sugar molecule are numbered as 1′, 2′, 3′, 4′, and 5′ (1′ is read as “one prime”).

Phosphate Group

The phosphate residue is attached to the hydroxyl group of the 5′ carbon of one sugar and the hydroxyl group of the 3′ carbon of the sugar of the next nucleotide, which forms a 5′3′ phosphodiester linkage. The phosphodiester linkage is not formed by simple dehydration reaction like the other linkages connecting monomers in macromolecules: its formation involves the removal of two phosphate groups. A polynucleotide may have thousands of such phosphodiester linkages.

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2.5.4: Amino Acids

An amino acid contains an amino group, a carboxyl group, and an R group, and it combines with other amino acids to form polypeptide chains.

Learning Objectives

- Describe the structure of an amino acid and the features that confer its specific properties

Key Points

- Each amino acid contains a central C atom, an amino group (NH2), a carboxyl group (COOH), and a specific R group.
- The R group determines the characteristics (size, polarity, and pH) for each type of amino acid.
- Peptide bonds form between the carboxyl group of one amino acid and the amino group of another through dehydration synthesis.
- A chain of amino acids is a polypeptide.

Key Terms

- **amino acid**: Any of 20 naturally occurring α-amino acids (having the amino, and carboxylic acid groups on the same carbon atom), and a variety of side chains, that combine, via peptide bonds, to form proteins.
- **R group**: The R group is a side chain specific to each amino acid that confers particular chemical properties to that amino acid.
- **polypeptide**: Any polymer of (same or different) amino acids joined via peptide bonds.

Structure of an Amino Acid

Amino acids are the monomers that make up proteins. Each amino acid has the same fundamental structure, which consists of a central carbon atom, also known as the alpha (α) carbon, bonded to an amino group (NH_2), a carboxyl group (COOH), and to a hydrogen atom. In the aqueous environment of the cell, the both the amino group and the carboxyl group are ionized under physiological conditions, and so have the structures $-NH_3^+$ and $-COO^-$, respectively. Every amino acid also has another atom or group of atoms bonded to the central atom known as the R group. This R group, or side chain, gives each amino acid proteins specific characteristics, including size, polarity, and pH.

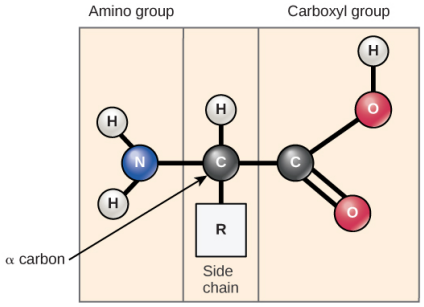

Figure: **Amino acid structure**: Amino acids have a central asymmetric carbon to which an amino group, a carboxyl group, a hydrogen atom, and a side chain (R group) are attached. This amino acid is unionized, but if it were placed in water at pH 7, its amino group would pick up another hydrogen and a positive charge, and the hydroxyl in its carboxyl group would lose and a hydrogen and gain a negative charge.

Types of Amino Acids

The name “amino acid” is derived from the amino group and carboxyl-acid-group in their basic structure. There are 21 amino acids present in proteins, each with a specific R group or side chain. Ten of these are considered essential amino acids in humans because the human body cannot produce them and they must be obtained from the diet. All organisms have different essential amino acids based on their physiology.

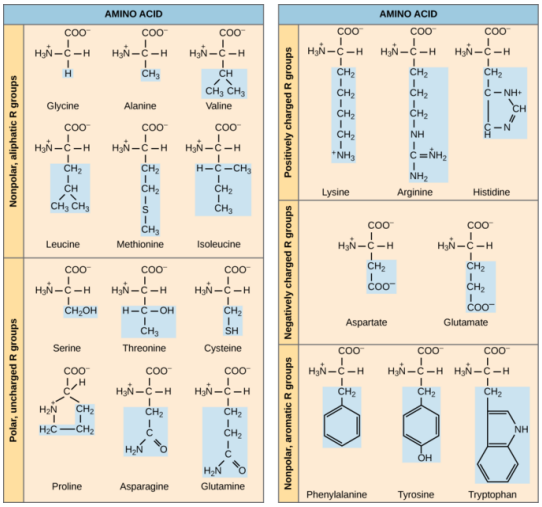

Figure: **Types of amino acids**: There are 21 common amino acids commonly found in proteins, each with a different R group (variant group) that determines its chemical nature. The 21st amino acid, not shown here, is selenocysteine, with an R group of -CH_2-SeH.

Characteristics of Amino Acids

Which categories of amino acid would you expect to find on the surface of a soluble protein, and which would you expect to find in the interior? What distribution of amino acids would you expect to find in a protein embedded in a lipid bilayer?

The chemical composition of the side chain determines the characteristics of the amino acid. Amino acids such as valine, methionine, and alanine are nonpolar (hydrophobic), while amino acids such as serine, threonine, and cysteine are polar (hydrophilic). The side chains of lysine and arginine are positively charged so these amino acids are also known as basic (high pH) amino acids. Proline is an exception to the standard structure of an amino acid because its R group is linked to the amino group, forming a ring-like structure.

Amino acids are represented by a single upper case letter or a three-letter abbreviation. For example, valine is known by the letter V or the three-letter symbol val.

Peptide Bonds

The sequence and the number of amino acids ultimately determine the protein's shape, size, and function. Each amino acid is attached to another amino acid by a covalent bond, known as a peptide bond. When two amino acids are covalently attached by a peptide bond, the carboxyl group of one amino acid and the amino group of the incoming amino acid combine and release a molecule of water. Any reaction that combines two monomers in a reaction that generates H_2O as one of the products is known as a dehydration reaction, so peptide bond formation is an example of a dehydration reaction.

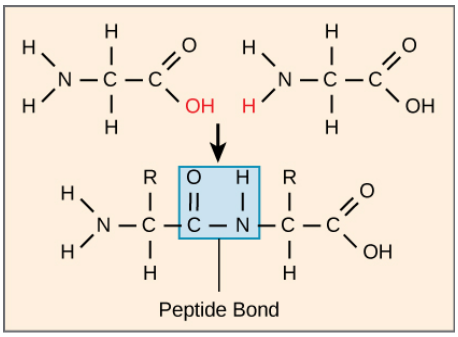

Figure: **Peptide bond formation**: Peptide bond formation is a dehydration synthesis reaction. The carboxyl group of one amino acid is linked to the amino group of the incoming amino acid. In the process, a molecule of water is released.

Polypeptide Chains

The resulting chain of amino acids is called a polypeptide chain. Each polypeptide has a free amino group at one end. This end is called the N terminal, or the amino terminal, and the other end has a free carboxyl group, also known as the C or carboxyl terminal.

When reading or reporting the amino acid sequence of a protein or polypeptide, the convention is to use the N-to-C direction. That is, the first amino acid in the sequence is assumed to the be one at the N terminal and the last amino acid is assumed to be the one at the C terminal.

Although the terms polypeptide and protein are sometimes used interchangeably, a polypeptide is technically any polymer of amino acids, whereas the term protein is used for a polypeptide or polypeptides that have folded properly, combined with any additional components needed for proper functioning, and is now functional.

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2.5.5: Types and Functions of Protiens

Proteins perform many essential physiological functions, including catalyzing biochemical reactions.

Learning Objectives

- Differentiate among the types and functions of proteins

Key Points

- Proteins are essential for the main physiological processes of life and perform functions in every system of the human body.
- A protein's shape determines its function.
- Proteins are composed of amino acid subunits that form polypeptide chains.
- Enzymes catalyze biochemical reactions by speeding up chemical reactions, and can either break down their substrate or build larger molecules from their substrate.
- The shape of an enzyme's active site matches the shape of the substrate.
- Hormones are a type of protein used for cell signaling and communication.

Key Terms

- **amino acid**: Any of 20 naturally occurring α-amino acids (having the amino, and carboxylic acid groups on the same carbon atom), and a variety of side chains, that combine, via peptide bonds, to form proteins.
- **polypeptide**: Any polymer of (same or different) amino acids joined via peptide bonds.
- **catalyze**: To accelerate a process.

Types and Functions of Proteins

Proteins perform essential functions throughout the systems of the human body. These long chains of amino acids are critically important for:

- catalyzing chemical reactions
- synthesizing and repairing DNA
- transporting materials across the cell
- receiving and sending chemical signals
- responding to stimuli
- providing structural support

Proteins (a polymer) are macromolecules composed of amino acid subunits (the monomers). These amino acids are covalently attached to one another to form long linear chains called polypeptides, which then fold into a specific three-dimensional shape. Sometimes these folded polypeptide chains are functional by themselves. Other times they combine with additional polypeptide chains to form the final protein structure. Sometimes non-polypeptide groups are also required in the final protein. For instance, the blood protein hemogobin is made up of four polypeptide chains, each of which also contains a heme molecule, which is ring structure with an iron atom in its center.

Proteins have different shapes and molecular weights, depending on the amino acid sequence. For example, hemoglobin is a globular protein, which means it folds into a compact globe-like structure, but collagen, found in our skin, is a fibrous protein, which means it folds into a long extended fiber-like chain. You probably look similar to your family members because you share similar proteins, but you look different from strangers because the proteins in your eyes, hair, and the rest of your body are different.

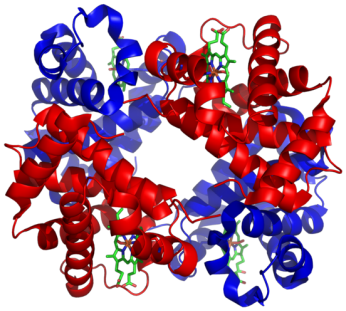

Figure: **Human Hemoglobin**: Structure of human hemoglobin. The proteins' α and β subunits are in red and blue, and the iron-containing heme groups in green. From the protein data base.

Because form determines function, any slight change to a protein's shape may cause the protein to become dysfunctional. Small changes in the amino acid sequence of a protein can cause devastating genetic diseases such as Huntington's disease or sickle cell anemia.

Enzymes

Enzymes are proteins that catalyze biochemical reactions, which otherwise would not take place. These enzymes are essential for chemical processes like digestion and cellular metabolism. Without enzymes, most physiological processes would proceed so slowly (or not at all) that life could not exist.

Because form determines function, each enzyme is specific to its substrates. The substrates are the reactants that undergo the chemical reaction catalyzed by the enzyme. The location where substrates bind to or interact with the enzyme is known as the active site, because that is the site where the chemistry occurs. When the substrate binds to its active site at the enzyme, the enzyme may help in its breakdown, rearrangement, or synthesis. By placing the substrate into a specific shape and microenvironment in the active site, the enzyme encourages the chemical reaction to occur. There are two basic classes of enzymes:

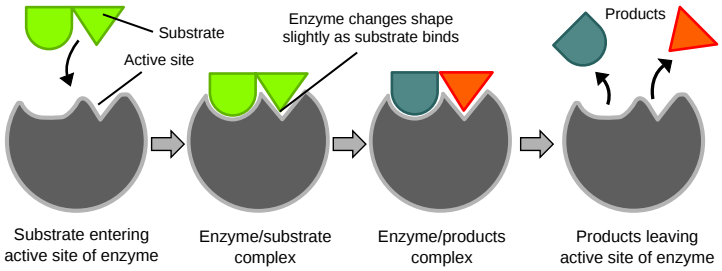

Figure: **Enzyme reaction**: A catabolic enzyme reaction showing the substrate matching the exact shape of the active site.

- Catabolic enzymes: enzymes that break down their substrate
- Anabolic enzymes: enzymes that build more complex molecules from their substrates

Enzymes are essential for digestion: the process of breaking larger food molecules down into subunits small enough to diffuse through a cell membrane and to be used by the cell. These enzymes include amylase, which catalyzes the digestion carbohydrates in the mouth and small intestine; pepsin, which catalyzes the digestion of proteins in the stomach; lipase, which catalyzes reactions need to emulsify fats in the small intestine; and trypsin, which catalyzes the further digestion of proteins in the small intestine.

Enzymes are also essential for biosynthesis: the process of making new, complex molecules from the smaller subunits that are provided to or generated by the cell. These biosynthetic enzymes include DNA Polymerase, which catalyzes the synthesis of new strands of the genetic material before cell division; fatty acid synthetase, which the synthesis of new fatty acids for fat or membrane lipid formation; and components of the ribosome, which catalyzes the formation of new polypeptides from amino acid monomers.

Hormones

Some proteins function as chemical-signaling molecules called hormones. These proteins are secreted by endocrine cells that act to control or regulate specific physiological processes, which include growth, development, metabolism, and reproduction. For example, insulin is a protein hormone that helps to regulate blood glucose levels. Other proteins act as receptors to detect the

concentrations of chemicals and send signals to respond. Some types of hormones, such as estrogen and testosterone, are lipid steroids, not proteins.

Other Protein Functions

Proteins perform essential functions throughout the systems of the human body. In the respiratory system, hemoglobin (composed of four protein subunits) transports oxygen for use in cellular metabolism. Additional proteins in the blood plasma and lymph carry nutrients and metabolic waste products throughout the body. The proteins actin and tubulin form cellular structures, while keratin forms the structural support for the dead cells that become fingernails and hair. Antibodies, also called immunoglobins, help recognize and destroy foreign pathogens in the immune system. Actin and myosin allow muscles to contract, while albumin nourishes the early development of an embryo or a seedling.

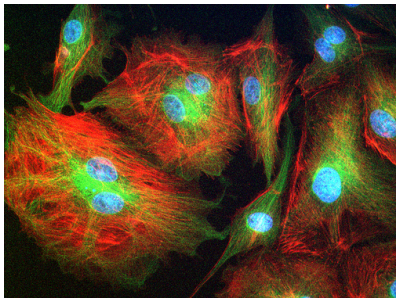

Figure: **Tubulin**: The structural protein tubulin stained red in mouse cells.

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2.5.6: ATP: Adenosine Triphosphate

Cells couple the exergonic reaction of ATP hydrolysis with endergonic reactions to harness the energy within the bonds of ATP.

Learning Objectives

- Explain the role of ATP as the currency of cellular energy

Key Points

- Adenosine triphosphate is composed of the nitrogenous base adenine, the five-carbon sugar ribose, and three phosphate groups.
- ATP is hydrolyzed to ADP in the reaction ATP+H2O→ADP+Pi+ free energy; the calculated ΔG for the hydrolysis of 1 mole of ATP is -57 kJ/mol.
- ADP is combined with a phosphate to form ATP in the reaction ADP+Pi+free energy→ATP+H2O.
- The energy released from the hydrolysis of ATP into ADP is used to perform cellular work, usually by coupling the exergonic reaction of ATP hydrolysis with endergonic reactions.
- Sodium-potassium pumps use the energy derived from exergonic ATP hydrolysis to pump sodium and potassium ions across the cell membrane while phosphorylation drives the endergonic reaction.

Key Terms

- **energy coupling**: Energy coupling occurs when the energy produced by one reaction or system is used to drive another reaction or system.
- **endergonic**: Describing a reaction that absorbs (heat) energy from its environment.
- **exergonic**: Describing a reaction that releases energy (heat) into its environment.
- **free energy**: Gibbs free energy is a thermodynamic potential that measures the useful or process-initiating work obtainable from a thermodynamic system at a constant temperature and pressure (isothermal, isobaric).
- **hydrolysis**: A chemical process of decomposition involving the splitting of a bond by the addition of water.

ATP: Adenosine Triphosphate

Adenosine triphosphate (ATP) is the energy currency for cellular processes. ATP provides the energy for both energy-consuming endergonic reactions and energy-releasing exergonic reactions, which require a small input of activation energy. When the chemical bonds within ATP are broken, energy is released and can be harnessed for cellular work. The more bonds in a molecule, the more potential energy it contains. Because the bond in ATP is so easily broken and reformed, ATP is like a rechargeable battery that powers cellular process ranging from DNA replication to protein synthesis.

Molecular Structure

Adenosine triphosphate (ATP) is comprised of the molecule adenosine bound to three phosphate groups. Adenosine is a nucleoside consisting of the nitrogenous base adenine and the five-carbon sugar ribose. The three phosphate groups, in order of closest to furthest from the ribose sugar, are labeled alpha, beta, and gamma. Together, these chemical groups constitute an energy powerhouse. The two bonds between the phosphates are equal high-energy bonds (phosphoanhydride bonds) that, when broken, release sufficient energy to power a variety of cellular reactions and processes. The bond between the beta and gamma phosphate is considered “high-energy” because when the bond breaks, the products [adenosine diphosphate (ADP) and one inorganic phosphate group (P_i)] have a lower free energy than the reactants (ATP and a water molecule). ATP breakdown into ADP and P_i is called hydrolysis because it consumes a water molecule (hydro-, meaning “water”, and lysis, meaning “separation”).

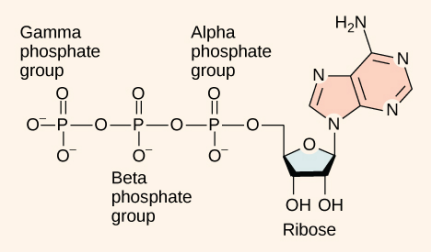

Figure: **Adenosine Triphosphate (ATP)**: ATP is the primary energy currency of the cell. It has an adenosine backbone with three phosphate groups attached.

ATP Hydrolysis and Synthesis

ATP is hydrolyzed into ADP in the following reaction:

$ATP + H_2O \rightarrow ADP + P_i + \text{free energy}$

Like most chemical reactions, the hydrolysis of ATP to ADP is reversible. The reverse reaction combines ADP + P_i to regenerate ATP from ADP. Since ATP hydrolysis releases energy, ATP synthesis must require an input of free energy.

ADP is combined with a phosphate to form ATP in the following reaction:

$ADP + P_i + \text{free energy} \rightarrow ATP + H_2O$

ATP and Energy Coupling

Exactly how much free energy (ΔG) is released with the hydrolysis of ATP, and how is that free energy used to do cellular work? The calculated ΔG for the hydrolysis of one mole of ATP into ADP and P_i is −7.3 kcal/mole (−30.5 kJ/mol). However, this is only true under standard conditions, and the ΔG for the hydrolysis of one mole of ATP in a living cell is almost double the value at standard conditions: 14 kcal/mol (−57 kJ/mol).

ATP is a highly unstable molecule. Unless quickly used to perform work, ATP spontaneously dissociates into ADP + P_i, and the free energy released during this process is lost as heat. To harness the energy within the bonds of ATP, cells use a strategy called energy coupling.

Energy Coupling in Sodium-Potassium Pumps

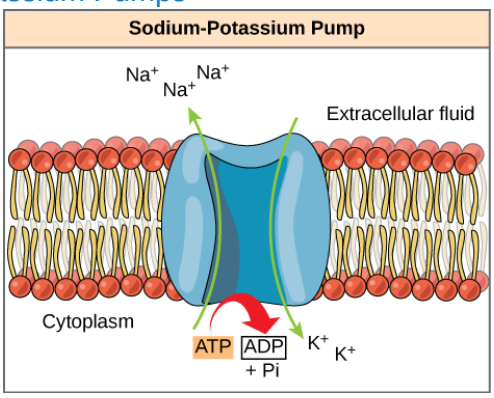

Figure: **Energy Coupling**: Sodium-potassium pumps use the energy derived from exergonic ATP hydrolysis to pump sodium and potassium ions across the cell membrane.

Cells couple the exergonic reaction of ATP hydrolysis with the endergonic reactions of cellular processes. For example, transmembrane ion pumps in nerve cells use the energy from ATP to pump ions across the cell membrane and generate an action potential. The sodium-potassium pump (Na^+/K^+ pump) drives sodium out of the cell and potassium into the cell. When ATP is hydrolyzed, it transfers its gamma phosphate to the pump protein in a process called phosphorylation. The Na^+/K^+ pump gains the free energy and undergoes a conformational change, allowing it to release three Na^+ to the outside of the cell. Two extracellular K^+ ions bind to the protein, causing the protein to change shape again and discharge the phosphate. By donating free energy to the Na^+/K^+ pump, phosphorylation drives the endergonic reaction.

Energy Coupling in Metabolism

During cellular metabolic reactions, or the synthesis and breakdown of nutrients, certain molecules must be altered slightly in their conformation to become substrates for the next step in the reaction series. In the very first steps of cellular respiration, glucose is broken down through the process of glycolysis. ATP is required for the phosphorylation of glucose, creating a high-energy but unstable intermediate. This phosphorylation reaction causes a conformational change that allows enzymes to convert the phosphorylated glucose molecule to the phosphorylated sugar fructose. Fructose is a necessary intermediate for glycolysis to move forward. In this example, the exergonic reaction of ATP hydrolysis is coupled with the endergonic reaction of converting glucose for use in the metabolic pathway.

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SECTION OVERVIEW

2.6: Energy

Topic hierarchy

2.6.1: Metabolism of Carbohydrates

2.6.2: Free Energy Changes in Chemical Reactions

2.6.3: Internal Energy and Enthaply

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2.6.1: Metabolism of Carbohydrates

Learning Objectives

- Analyze the importance of carbohydrate metabolism to energy production

Metabolism of Carbohydrates

Carbohydrates are one of the major forms of energy for animals and plants. Plants build carbohydrates using light energy from the sun (during the process of photosynthesis), while animals eat plants or other animals to obtain carbohydrates. Plants store carbohydrates in long polysaccharides chains called starch, while animals store carbohydrates as the molecule glycogen. These large polysaccharides contain many chemical bonds and therefore store a lot of chemical energy. When these molecules are broken down during metabolism, the energy in the chemical bonds is released and can be harnessed for cellular processes.



Figure: **All living things use carbohydrates as a form of energy.**: Plants, like this oak tree and acorn, use energy from sunlight to make sugar and other organic molecules. Both plants and animals (like this squirrel) use cellular respiration to derive energy from the organic molecules originally produced by plants

Energy Production from Carbohydrates (Cellular Respiration)

The metabolism of any monosaccharide (simple sugar) can produce energy for the cell to use. Excess carbohydrates are stored as starch in plants and as glycogen in animals, ready for metabolism if the energy demands of the organism suddenly increase. When those energy demands increase, carbohydrates are broken down into constituent monosaccharides, which are then distributed to all the living cells of an organism. Glucose ($C_6H_{12}O_6$) is a common example of the monosaccharides used for energy production.

Inside the cell, each sugar molecule is broken down through a complex series of chemical reactions. As chemical energy is released from the bonds in the monosaccharide, it is harnessed to synthesize high-energy adenosine triphosphate (ATP) molecules. ATP is the primary energy currency of all cells. Just as the dollar is used as currency to buy goods, cells use molecules of ATP to perform immediate work and power chemical reactions.

The breakdown of glucose during metabolism is call cellular respiration can be described by the equation:

$$\mathrm{C_6H_{12}O_6 + 6\,O_2 \rightarrow 6\,CO_2 + 6\,H_2O + energy} \tag{2.6.1.1}$$

Producing Carbohydrates (Photosynthesis)

Plants and some other types of organisms produce carbohydrates through the process called photosynthesis. During photosynthesis, plants convert light energy into chemical energy by building carbon dioxide gas molecules (CO_2) into sugar molecules like glucose. Because this process involves building bonds to synthesize a large molecule, it requires an input of energy (light) to proceed. The synthesis of glucose by photosynthesis is described by this equation (notice that it is the reverse of the previous equation):

$$\mathrm{6\,CO_2 + 6\,H_2O + energy \rightarrow C_6H_{12}O_6 + 6\,O_2} \tag{2.6.1.2}$$

As part of plants' chemical processes, glucose molecules can be combined with and converted into other types of sugars. In plants, glucose is stored in the form of starch, which can be broken down back into glucose via cellular respiration in order to supply ATP.

Key Points

- The breakdown of glucose living organisms utilize to produce energy is described by the equation:

$$\mathrm{C_6H_{12}O_6 + 6\,O_2 \rightarrow 6\,CO_2 + 6\,H_2O + energy}$$

- The photosynthetic process plants utilize to synthesize glucose is described by the equation:

$$6\,CO_2 + 6\,H_2O + \text{energy} \rightarrow C_6H_{12}O_6 + 6\,O_2$$

- Glucose that is consumed is used to make energy in the form of ATP, which is used to perform work and power chemical reactions in the cell.
- During photosynthesis, plants convert light energy into chemical energy that is used to build molecules of glucose.

Key Terms

- **adenosine triphosphate**: a multifunctional nucleoside triphosphate used in cells as a coenzyme, often called the “molecular unit of energy currency” in intracellular energy transfer
- **glucose**: a simple monosaccharide (sugar) with a molecular formula of C6H12O6C6H12O6C6H12O6; it is a principal source of energy for cellular metabolism

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2.6.2: Free Energy Changes in Chemical Reactions

ΔG determines the direction and extent of chemical change.

Learning Objectives

- Recall the possible free energy changes for chemical reactions.

Key Points

- If the free energy of the reactants is greater than that of the products, the entropy of the world will increase when the reaction takes place as written, and so the reaction will tend to take place spontaneously.
- If the free energy of the products exceeds that of the reactants, then the reaction will not take place.
- An important consequence of the one-way downward path of the free energy is that once it reaches its minimum possible value, net change comes to a halt.
- In a spontaneous change, Gibbs energy always decreases and never increases.

Key Terms

- **spontaneous change**: A spontaneous process is the time-evolution of a system in which it releases free energy (usually as heat) and moves to a lower, more thermodynamically stable energy state.

The Direction and Extent of Chemical Change

ΔG determines the direction and extent of chemical change. Remember that ΔG is meaningful only for changes in which the temperature and pressure remain constant. These are the conditions under which most reactions are carried out in the laboratory. The system is usually open to the atmosphere (constant pressure) and the process is started and ended at room temperature (after any heat that has been added or which was liberated by the reaction has dissipated.)

The importance of the Gibbs function can hardly be over-stated: it determines whether a given chemical change is thermodynamically possible. Thus, if the free energy of the reactants is greater than that of the products, the entropy of the world will increase and the reaction takes place spontaneously. Conversely, if the free energy of the products exceeds that of the reactants, the reaction will not take place.

In a spontaneous change, Gibbs energy always decreases and never increases. This of course reflects the fact that the entropy of the world behaves in the exact opposite way (owing to the negative sign in the TΔS term). Here is an example:

H2O(liquid)→H2O(ice)H2O(liquid)→H2O(ice)

Water below zero degrees Celsius undergoes a decrease in its entropy, but the heat released into the surroundings more than compensates for this so the entropy of the world increases, the free energy of the H_2O diminishes, and the process proceeds spontaneously.

An important consequence of the one-way downward path of the free energy is that once it reaches its minimum possible value, net change comes to a halt. This, of course, represents the state of chemical equilibrium. These relations are summarized as follows:

- ΔG<0ΔG<0: The reaction will occur spontaneously to the right.
- ΔG>0ΔG>0: The reaction will occur spontaneously to the left.
- ΔG=0ΔG=0: The reaction is at equilibrium and will not proceed in either direction.

Conditions for Spontaneous Change

Recall the condition for spontaneous change:

$\Delta G = \Delta H - T\Delta S < 0$

where ΔG = change in Gibbs free energy, ΔH = change in enthalpy, T = absolute temperature, and ΔS = change in entropy

It is apparent that the temperature dependence of ΔG depends almost entirely on the entropy change associated with the process. (it is appropriate to say “almost” because the values of ΔH and ΔS are themselves slightly temperature dependent; both gradually increase with temperature). In particular, notice that in the above equation the sign of the entropy change determines whether the reaction becomes more or less spontaneous as the temperature is raised.

For any given reaction, the sign of ΔH can also be positive or negative. This means that there are four possibilities for the influence that temperature can have on the spontaneity of a process:

Case 1: ΔH < 0 and ΔS > 0

Under these conditions, both the ΔH and TΔS terms will be negative, so ΔG will be negative regardless of the temperature. An exothermic reaction whose entropy increases will be spontaneous at all temperatures.

Case 2: ΔH < 0 and ΔS < 0

If the reaction is sufficiently exothermic it can force ΔG to be negative only at temperatures below which $|T\Delta S| < |\Delta H|$. This means that there is a temperature defined by $T=\Delta H \Delta S T=\Delta H \Delta S$ at which the reaction is at equilibrium; the reaction will only proceed spontaneously below this temperature. The freezing of a liquid or the condensation of a gas are the most common examples of this condition.

Case 3: ΔH > 0 and ΔS > 0

This is the reverse of the previous case; the entropy increase must overcome the handicap of an endothermic process so that $T\Delta S > \Delta H$. Since the effect of the temperature is to "magnify" the influence of a positive ΔS, the process will be spontaneous at temperatures above $T=\Delta H \Delta S T=\Delta H \Delta S$. (Think of melting and boiling.)

Case 4: ΔH > 0 and ΔS < 0

With both ΔH and ΔS working against it, this kind of process will not proceed spontaneously at any temperature. Substance A always has a greater number of accessible energy states, and is therefore always the preferred form.

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2.6.3: Internal Energy and Enthaply

The enthalpy of reaction measures the heat released/absorbed by a reaction that occurs at constant pressure.

Learning Objectives

- Review enthalpy of reaction

Key Points

- At constant volume, the heat of reaction is equal to the change in the internal energy of the system.
- At constant pressure, the heat of reaction is equal to the enthalpy change of the system.
- Most chemical reactions occur at constant pressure, so enthalpy is more often used to measure heats of reaction than internal energy.

Key Terms

- **enthalpy**: In thermodynamics, a measure of the heat content of a chemical or physical system.
- **internal energy**: A property characteristic of the state of a thermodynamic system, the change in which is equal to the heat absorbed minus the work done by the system.
- **first law of thermodynamics**: Heat and work are forms of energy transfer; the internal energy of a closed system changes as heat and work are transferred into or out of it.

In thermodynamics, work (W) is defined as the process of an energy transfer from one system to another. The first law of thermodynamics states that the energy of a closed system is equal to the amount of heat supplied to the system minus the amount of work done by the system on its surroundings. The amount of energy for a closed system is written as follows:

$\Delta U = Q - W \Delta U = Q - W$

In this equation, U is the total energy of the system, Q is heat, and W is work. In chemical systems, the most common type of work is pressure-volume (PV) work, in which the volume of a gas changes. Substituting this in for work in the above equation, we can define the change in internal energy for a chemical system:

$\Delta U = Q - P\Delta V \Delta U = Q - P\Delta V$

Internal Energy Change at Constant Volume

Let's examine the internal energy change, $\Delta U \Delta U$, at constant volume. At constant volume, $\Delta V = 0 \Delta V = 0$, the equation for the change in internal energy reduces to the following:

$\Delta U = Q_V \Delta U = Q_V$

The subscript V is added to Q to indicate that this is the heat transfer associated with a chemical process at constant volume. This internal energy is often very difficult to calculate in real life settings, though, because chemists tend to run their reactions in open flasks and beakers that allow gases to escape to the atmosphere. Therefore, volume is not held constant, and calculating $\Delta U \Delta U$ becomes problematic. To correct for this, we introduce the concept of *enthalpy*, which is much more commonly used by chemists.

Standard Enthalpy of Reaction

The enthalpy of reaction is defined as the internal energy of the reaction system, *plus* the product of pressure and volume. It is given by:

$H = U + PV H = U + PV$

By adding the PV term, it becomes possible to measure a change in energy within a chemical system, even when that system does work on its surroundings. Most often, we are interested in the change in enthalpy of a given reaction, which can be expressed as follows:

$\Delta H = \Delta U + P\Delta V \Delta H = \Delta U + P\Delta V$

When you run a chemical reaction in a laboratory, the reaction occurs at constant pressure, because the atmospheric pressure around us is relatively constant. We will examine the change in enthalpy for a reaction at constant pressure, in order to see why enthalpy is such a useful concept for chemists.

Enthalpy of Reaction at Constant Pressure

Let's look once again at the change in enthalpy for a given chemical process. It is given as follows:

$\Delta H = \Delta U + P\Delta V \Delta H = \Delta U + P\Delta V$

However, we also know that:

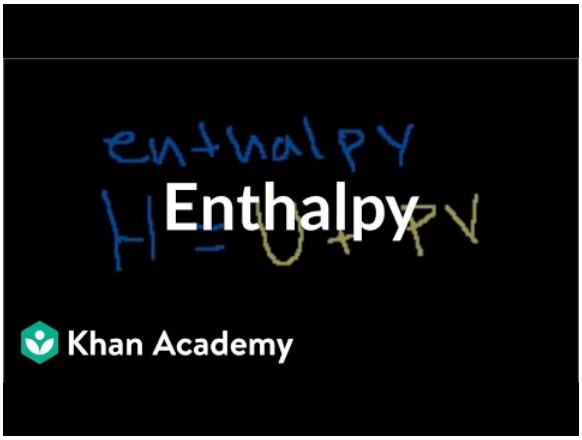
$\Delta U = Q - W = Q - P\Delta V \Delta U = Q - W = Q - P\Delta V$

Substituting to combine these two equations, we have:

$\Delta H = Q - P\Delta V + P\Delta V = QP \Delta H = Q - P\Delta V + P\Delta V = QP$

Thus, at constant pressure, the change in enthalpy is simply equal to the heat released/absorbed by the reaction. Due to this relation, the change in enthalpy is often referred to simply as the "heat of reaction."





Enthalpy: An explanation of why enthalpy can be viewed as "heat content" in a constant pressure system.

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SECTION OVERVIEW

2.7: Enzymes

Topic hierarchy

2.7.1: Control of Metabolism Through Enzyme Regulation

2.7.2: Enzyme Active Site and Substrate Specificity

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2.7.1: Control of Metabolism Through Enzyme Regulation

Learning Objectives

- Explain the effect of an enzyme on chemical equilibrium

Control of Metabolism Through Enzyme Regulation

Cellular needs and conditions vary from cell to cell and change within individual cells over time. For example, a stomach cell requires a different amount of energy than a skin cell, fat storage cell, blood cell, or nerve cell. The same stomach cell may also need more energy immediately after a meal and less energy between meals.

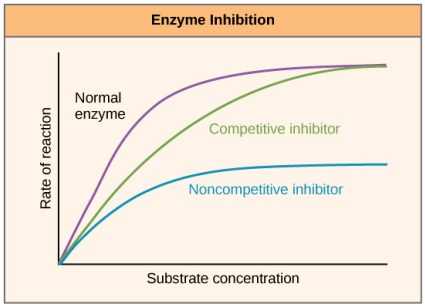

Figure: **Enzyme inhibition**: Competitive and noncompetitive inhibition affect the rate of reaction differently. Competitive inhibitors affect the initial rate, but do not affect the maximal rate, whereas noncompetitive inhibitors affect the maximal rate.

A cell's function is encapsulated by the chemical reactions it can carry out. Enzymes lower the activation energies of chemical reactions; in cells, they promote those reactions that are specific to the cell's function. Because enzymes ultimately determine which chemical reactions a cell can carry out and the rate at which they can proceed, they are key to cell functionality.

Competitive and Noncompetitive Inhibition

The cell uses specific molecules to regulate enzymes in order to promote or inhibit certain chemical reactions. Sometimes it is necessary to inhibit an enzyme to reduce a reaction rate, and there is more than one way for this inhibition to occur. In competitive inhibition, an inhibitor molecule is similar enough to a substrate that it can bind to the enzyme's active site to stop it from binding to the substrate. It "competes" with the substrate to bind to the enzyme.

In noncompetitive inhibition, an inhibitor molecule binds to the enzyme at a location other than the active site (an allosteric site). The substrate can still bind to the enzyme, but the inhibitor changes the shape of the enzyme so it is no longer in optimal position to catalyze the reaction.

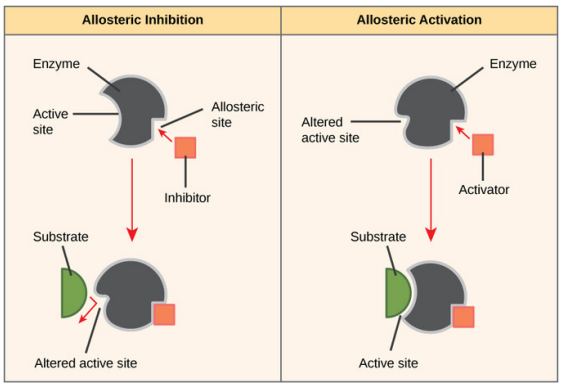

Figure: **Allosteric inhibitors and activators**: Allosteric inhibitors modify the active site of the enzyme so that substrate binding is reduced or prevented. In contrast, allosteric activators modify the active site of the enzyme so that the affinity for the substrate increases.

Allosteric Inhibition and Activation

In noncompetitive allosteric inhibition, inhibitor molecules bind to an enzyme at the allosteric site. Their binding induces a conformational change that reduces the affinity of the enzyme's active site for its substrate. The binding of this allosteric inhibitor

changes the conformation of the enzyme and its active site, so the substrate is not able to bind. This prevents the enzyme from lowering the activation energy of the reaction, and the reaction rate is reduced.

However, allosteric inhibitors are not the only molecules that bind to allosteric sites. Allosteric activators can increase reaction rates. They bind to an allosteric site which induces a conformational change that *increases* the affinity of the enzyme's active site for its substrate. This increases the reaction rate.

Cofactors and Coenzymes

Many enzymes only work if bound to non-protein helper molecules called cofactors and coenzymes. Binding to these molecules promotes optimal conformation and function for their respective enzymes. These molecules bind temporarily through ionic or hydrogen bonds or permanently through stronger covalent bonds.

Cofactors are inorganic ions such as iron (Fe^{2+}) and magnesium (Mg^{2+}). For example, DNA polymerase requires a zinc ion (Zn^{2+}) to build DNA molecules. Coenzymes are organic helper molecules with a basic atomic structure made up of carbon and hydrogen. The most common coenzymes are dietary vitamins. Vitamin C is a coenzyme for multiple enzymes that take part in building collagen, an important component of connective tissue. Pyruvate dehydrogenase is a complex of several enzymes that requires one cofactor and five different organic coenzymes to catalyze its chemical reaction. The availability of various cofactors and coenzymes regulates enzyme function.

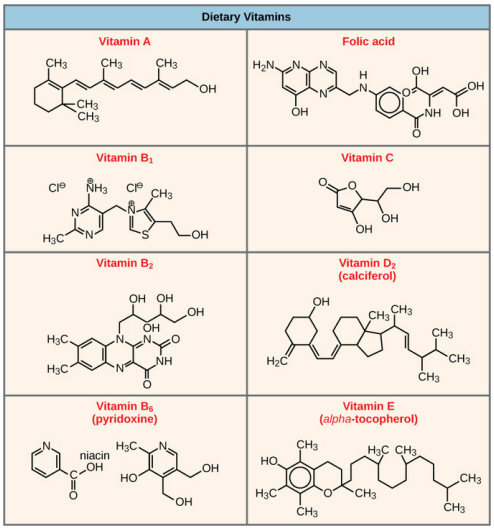

Figure: **Vitamins**: Vitamins are important coenzymes or precursors of coenzymes and are required for enzymes to function properly. Multivitamin capsules usually contain mixtures of all the vitamins at different percentages.

Enzyme Compartmentalization

In eukaryotic cells, molecules such as enzymes are usually compartmentalized into different organelles. This organization contributes to enzyme regulation because certain cellular processes are contained in separate organelles. For example, the enzymes involved in the later stages of cellular respiration carry out reactions exclusively in the mitochondria. The enzymes involved in the digestion of cellular debris and foreign materials are located within lysosomes.

Feedback Inhibition in Metabolic Pathways

Feedback inhibition is when a reaction product is used to regulate its own further production. Cells have evolved to use feedback inhibition to regulate enzyme activity in metabolism, by using the products of the enzymatic reactions to inhibit further enzyme activity. Metabolic reactions, such as anabolic and catabolic processes, must proceed according to the demands of the cell. In order to maintain chemical equilibrium and meet the needs of the cell, some metabolic products inhibit the enzymes in the chemical pathway while some reactants activate them.

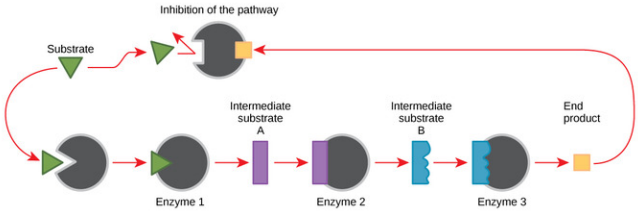

Figure: **Feedback inhibition**: Metabolic pathways are a series of reactions catalyzed by multiple enzymes. Feedback inhibition, where the end product of the pathway inhibits an earlier step, is an important regulatory mechanism in cells.

The production of both amino acids and nucleotides is controlled through feedback inhibition. For an example of feedback inhibition, consider ATP. It is the product of the catabolic metabolism of sugar (cellular respiration), but it also acts as an allosteric regulator for the same enzymes that produced it. ATP is an unstable molecule that can spontaneously dissociate into ADP; if too much ATP were present, most of it would go to waste. This feedback inhibition prevents the production of additional ATP if it is already abundant. However, while ATP is an inhibitor, ADP is an allosteric activator. When levels of ADP are high compared to ATP levels, ADP triggers the catabolism of sugar to produce more ATP.

Key Points

- In competitive inhibition, an inhibitor molecule competes with a substrate by binding to the enzyme ‘s active site so the substrate is blocked.
- In noncompetitive inhibition (also known as allosteric inhibition), an inhibitor binds to an allosteric site; the substrate can still bind to the enzyme, but the enzyme is no longer in optimal position to catalyze the reaction.
- Allosteric inhibitors induce a conformational change that changes the shape of the active site and reduces the affinity of the enzyme’s active site for its substrate.
- Allosteric activators induce a conformational change that changes the shape of the active site and increases the affinity of the enzyme’s active site for its substrate.
- Feedback inhibition involves the use of a reaction product to regulate its own further production.
- Inorganic cofactors and organic coenzymes promote optimal enzyme orientation and function.
- Vitamins act as coenzymes (or precursors to coenzymes) and are necessary for enzymes to function.

Key Terms

- **coenzyme**: An organic molecule that is necessary for an enzyme to function.
- **allosteric site**: A site other than the active site on an enzyme.
- **cofactor**: An inorganic molecule that is necessary for an enzyme to function.

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2.7.2: Enzyme Active Site and Substrate Specificity

Enzymes catalyze chemical reactions by lowering activation energy barriers and converting substrate molecules to products.

Learning Objectives

- Describe models of substrate binding to an enzyme's active site.

Key Points

- The enzyme 's active site binds to the substrate.
- Increasing the temperature generally increases the rate of a reaction, but dramatic changes in temperature and pH can denature an enzyme, thereby abolishing its action as a catalyst.
- The induced fit model states an substrate binds to an active site and both change shape slightly, creating an ideal fit for catalysis.
- When an enzyme binds its substrate it forms an enzyme-substrate complex.
- Enzymes promote chemical reactions by bringing substrates together in an optimal orientation, thus creating an ideal chemical environment for the reaction to occur.
- The enzyme will always return to its original state at the completion of the reaction.

Key Terms

- **substrate**: A reactant in a chemical reaction is called a substrate when acted upon by an enzyme.
- **induced fit**: Proposes that the initial interaction between enzyme and substrate is relatively weak, but that these weak interactions rapidly induce conformational changes in the enzyme that strengthen binding.
- **active site**: The active site is the part of an enzyme to which substrates bind and where a reaction is catalyzed.

Enzyme Active Site and Substrate Specificity

Enzymes bind with chemical reactants called substrates. There may be one or more substrates for each type of enzyme, depending on the particular chemical reaction. In some reactions, a single-reactant substrate is broken down into multiple products. In others, two substrates may come together to create one larger molecule. Two reactants might also enter a reaction, both become modified, and leave the reaction as two products.

The enzyme's active site binds to the substrate. Since enzymes are proteins, this site is composed of a unique combination of amino acid residues (side chains or R groups). Each amino acid residue can be large or small; weakly acidic or basic; hydrophilic or hydrophobic; and positively-charged, negatively-charged, or neutral. The positions, sequences, structures, and properties of these residues create a very specific chemical environment within the active site. A specific chemical substrate matches this site like a jigsaw puzzle piece and makes the enzyme specific to its substrate.

Active Sites and Environmental Conditions

Environmental conditions can affect an enzyme's active site and, therefore, the rate at which a chemical reaction can proceed. Increasing the environmental temperature generally increases reaction rates because the molecules are moving more quickly and are more likely to come into contact with each other.

However, increasing or decreasing the temperature outside of an optimal range can affect chemical bonds within the enzyme and change its shape. If the enzyme changes shape, the active site may no longer bind to the appropriate substrate and the rate of reaction will decrease. Dramatic changes to the temperature and pH will eventually cause enzymes to denature.

Induced Fit and Enzyme Function

For many years, scientists thought that enzyme-substrate binding took place in a simple "lock-and-key" fashion. This model asserted that the enzyme and substrate fit together perfectly in one instantaneous step. However, current research supports a more refined view called induced fit. As the enzyme and substrate come together, their interaction causes a mild shift in the enzyme's structure that confirms an ideal binding arrangement between the enzyme and the substrate. This dynamic binding maximizes the enzyme's ability to catalyze its reaction.

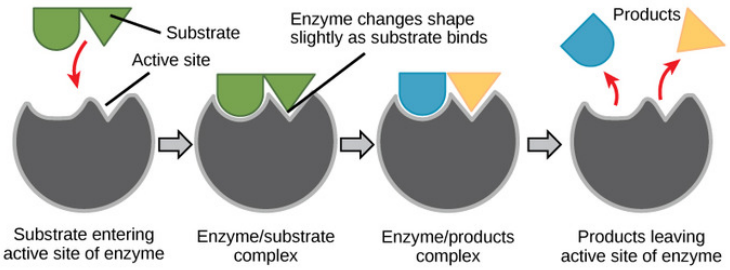

Figure: **Induced Fit**: According to the induced fit model, both enzyme and substrate undergo dynamic conformational changes upon binding. The enzyme contorts the substrate into its transition state, thereby increasing the rate of the reaction.

Enzyme-Substrate Complex

When an enzyme binds its substrate, it forms an enzyme-substrate complex. This complex lowers the activation energy of the reaction and promotes its rapid progression by providing certain ions or chemical groups that actually form covalent bonds with molecules as a necessary step of the reaction process. Enzymes also promote chemical reactions by bringing substrates together in an optimal orientation, lining up the atoms and bonds of one molecule with the atoms and bonds of the other molecule. This can contort the substrate molecules and facilitate bond-breaking. The active site of an enzyme also creates an ideal environment, such as a slightly acidic or non-polar environment, for the reaction to occur. The enzyme will always return to its original state at the completion of the reaction. One of the important properties of enzymes is that they remain ultimately unchanged by the reactions they catalyze. After an enzyme is done catalyzing a reaction, it releases its products (substrates).

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CHAPTER OVERVIEW

3: Microscopy

3.1: Looking at Microbes

3.1A: Microbe Size

3.1B: Units of Measurement for Microbes

3.1C: Refraction and Magnification

3.1D: Magnification and Resolution

3.2: Other Types of Microscopy

3.2A: Microscopy

3.2B: General Staining Methods

3.3: Other Types of Microscopy

3.3A: Dark-Field Microscopy

3.3B: Phase-Contrast Microscopy

3.3C: Interference Microscopy

3.3D: Fluorescence Microscopy

3.3E: Confocal Micropscopy

3.3F: Electron Microscopy

3.3G: Scanned-Probe Microscopy

3.3H: X-Ray Diffraction Analysis

Thumbnail: A compound microscope in a Biology lab. (CC -BY-SA 4.0; Acagastya).

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SECTION OVERVIEW

3.1: Looking at Microbes

Topic hierarchy

3.1A: Microbe Size

3.1B: Units of Measurement for Microbes

3.1C: Refraction and Magnification

3.1D: Magnification and Resolution

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3.1A: Microbe Size

Microbes are often very small, even in comparison to microscopic cells from animals.

Learning Objectives

- Recall the size of microbes in comparison to human cells and viruses

Key Points

- Microbes are generally described as being microscopic in size. Therefore, they are smaller than a human eye can see.
- The size of microbes can be hard to imagine because they are so small. In comparison to animal cells, microbes tend to be smaller. They are about 1/10th the size of a typical human cell.
- Microbes are generally measured in the scale of one millionth of a meter, which is known as a micrometer.

Key Terms

- **protozoan**: Any of the diverse group of eukaryotes, of the phylum Protozoa, that are primarily unicellular, existing singly or aggregating into colonies, are usually nonphotosynthetic, and are often classified further into phyla according to their capacity for and means of motility, as by pseudopods, flagella, or cilia.
- **macroscopic**: Visible to the unassisted eye.

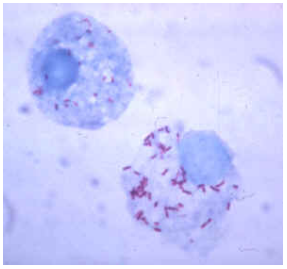

Figure: **A Microbe versus Animal Cell**: The large spheres are tick cells. The purple bars and dots are the bacterium Rickettsia rickettsii, which is the causative agent of Rocky Mountain spotted fever. Rickettsia rickettsii is a small bacterium that grows inside the cells of its hosts. These bacteria range in size from 0.2 x 0.5 micrometers to 0.3 x 2.0 micrometers.

Microbiology is the study of microbes. The name of the field is driven by the tool that largely determines if something is a microbe. Basically, microbiology is the study of organisms that one needs to use a microscope to visualize. Of course, there are exceptions. There are types of microscopes that visualize to the atomic level, which is significantly smaller than microbes. Alternatively, there are single cell organisms, such as some types of green algae and some protozoans that are generally studied by microbiologists. These are macroscopic or view-able without a microscope.



Figure: **Ventricaria ventricosa**: Ventricaria ventricosa is one of the largest known unicellular organisms. They about the size of a ping pong ball.

The size of microbes can be hard to imagine because they are so small in comparison to what most people see day to day. Even in comparison to animal cells, microbes tend to be smaller. They are about 1/10th the size of a typical human cell. So, a microbe such as a bacteria cell would be the size of a cat or small dog in comparison to a human-sized animal-cell. Viruses are about 1/10th the size of other microbes such as bacteria. Therefore, if a bacteria is the size of cat, then a virus would be about the size of a mouse.

To put a numerical value on microbial size, most measurements of microbes are done with the unit of measure of micrometer, which is one millionth of a meter (one 2,500th of an inch). In relation to something more tangible a period or “. ” is about 0.5

millimeters or 0.5/1,000th of a meter. A typical microbe would be about 1/500th of a period.

Of course there are exceptions. Some unicellular organisms studied by microbiologists are macroscopic. This includes *Valonia ventricosa*, which can be up to 5 cm in length. It is a member of the Chlorophyta phylum which are a sub-group of green algae. Many types of green algae are not microscopic, but they are often studied by microbiologists.

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3.1B: Units of Measurement for Microbes

Measuring microbes presents challenges because they are very small, requiring indirect measures of microbes to understand them better.

Learning Objectives

- Recognize the methods used to measure microbial growth

Key Points

- Understanding microbiological life means quantifying it. Since microbes are so small, this is a challenge.
- The size of a microbe is usually measured in micrometers, or one millionth of a meter.
- There are many aspects of microbes that can be measured in addition to size, including metric like genome size and growth rates.

Key Terms

- **flow cytometry**: A technique used to sort and classify cells by using fluorescent markers on their surface.
- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

Microbes are broadly defined as organisms that are microscopic. As a result, measuring them can be very difficult. The units used to describe objects on a microscopic length scale are most commonly the Micrometer (oi) – one millionth of 1 meter and smaller units. Most microbes are around 1 micrometer in size. Viruses are typically $1/10^{th}$ that size. Animal cells are typically around 10 micrometers in size. However, length is not the only measurement that pertains to microbes. Microbes have genomes and these are typically smaller than the genomes of macroscopic organisms such as humans. DNA is measured in base pairs of DNA. For example, the human genome is about 3.4 billion base pairs while the common intestinal bacteria *Escherichia coli* is 4.6 million base pairs. Additionally, microbes are usually not weighed individually, but can be as an aggregate for various experiments. An estimate of the weight of an individual microbe can be made by estimating the number of microbes. This is especially important for biomass studies where the units of measurement are in units like picog, 10^{-12} of a kilogram (Kg), nanogram 10^{-9} of a Kg, and microgram, 10^{-6} of a Kg (a kilogram is a little over 2 pounds).

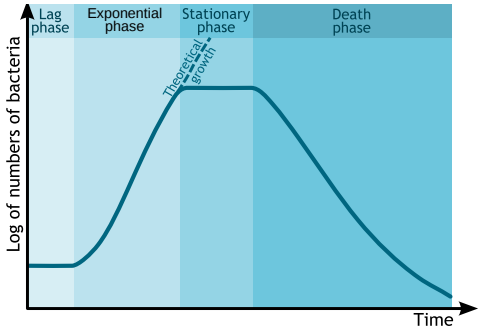

Figure: **Bacterial Growth Curve**: This chart shows the logarithmic growth of bacteria. Note the Y-axis scale is logarithmic meaning that the number represents doubling. The phases of growth are labelled on top.

Microbial growth is an important measure in understanding microbes. Microbial growth is the division of one microbe into two daughter cells in a process called binary fission. As a result, “local doubling” of the microbial population occurs. Both daughter cells from the division do not necessarily survive. However, if the number surviving exceeds unity on average, the microbial population undergoes exponential growth. The measurement of an exponential microbial growth curve in batch culture was traditionally a part of the training of all microbiologists; The basic means requires bacterial enumeration (cell counting) by direct and individual (microscopic, flow cytometry), direct and bulk (biomass), indirect and individual (colony counting), or indirect and bulk (most probable number, turbidity, nutrient uptake) methods. Since there are limits on space, food, and other factors, actual growth never matches actual measured growth.

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3.1C: Refraction and Magnification

Learning Objectives

- Describe refraction and distinguish between convex and concave lenses

The underlying principal of a microscope is that lenses refract light which allows for magnification. Refraction occurs when light travels through an area of space that has a changing index of refraction. The simplest case of refraction occurs when there is an interface between a uniform medium with an index of refraction and another medium with an index of refraction.

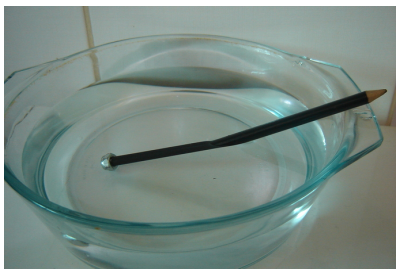

Figure: ***Refraction****: As the light is reflected off the pencil we see that, due to the different refraction indexes of water and air, the pencil appears to bend in the water. However, the pencil is straight. It is actually the water acting much like a lens in a microscope that gives it the appearance of bending.*

Some media have an index of refraction that varies gradually with position. Therefore, light rays curve through the medium rather than travelling in straight lines. This effect is what is responsible for mirages seen on hot days where the changing index of refraction of the air causes the light rays to bend creating the appearance of *specular reflections* in the distance (as if on the surface of a pool of water).

Taking advantage of the principle of refraction, devices can be built that can focus light. A device that produces converging or diverging light rays due to refraction is known as a lens. In general, two types of lenses exist: *convex lenses*, which cause parallel light rays to converge, and *concave lenses*, which cause parallel light rays to diverge. The former property of convex lenses is of special interest to microbiologists. In essence, a convex lens allows magnification. Light reflecting off an object is focused to a point. The simplest example of this that most people know is a magnifying glass. A magnifying glass is one convex lens, and this by itself allows the magnification of objects.

A microscope is basically a series of lenses that take advantage of the nature of refraction. Due to the nature of light, and the maximum amount of refraction that can be possible by a material, there are limits to the amount of magnification that can be done by a light microscope.

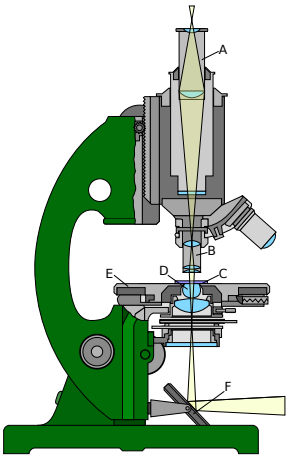

Figure: ***The Microscope****: Notice the blue areas, which represent lenses. Note also that many of the lenses are convex, thus the light that goes through a specimen is focused and therefore magnified. Labels: A) Ocular, B) Objective, C) slide holder, D) Illumination Lenses, E) Slide Stage, and F) Illumination Mirror*

Summary

- Convex lenses allow light to converge.
- Concave lenses spread light that travels through it.
- There are limits to the amount of refraction that can be done by a material, and therefore, limits to the amount a microscope can magnify a sample.

Key Terms

- **concave**: Curved like the inner surface of a sphere or bowl.
- **convex**: Curved or bowed outward like the outside of a bowl or sphere or circle.
- **specular**: Pertaining to mirrors; mirror-like, reflective.

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3.1D: Magnification and Resolution

Magnification is the enlargement of an image; resolution is the ability to tell two objects apart.

Learning Objectives

- Define magnification and resolution

Key Points

- Magnification is the ability to make small objects seem larger, such as making a microscopic organism visible.
- Resolution is the ability to distinguish two objects from each other.
- Light microscopy has limits to both its resolution and its magnification.

Key Terms

- **airy disks**: In optics, the Airy disk (or Airy disc) and Airy pattern are descriptions of the best-focused spot of light that a perfect lens with a circular aperture can make, limited by the diffraction of light.
- **diffraction**: the breaking up of an electromagnetic wave as it passes a geometric structure (e.g., a slit), followed by reconstruction of the wave by interference

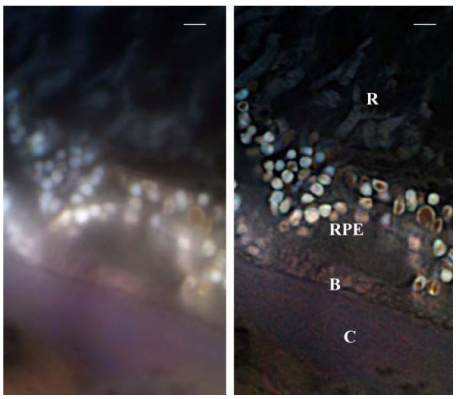

Figure: **Aging Tissue and Vision Loss**: These are micrographs of a section of a human eye. Using computer algorithms and other technology the panel on the right has a higher resolution and is therefore clearer. It should be noted that both panels are at the same magnification, yet the panel on the right has a higher resolution and gives more information on the sample. The labels represent various parts of the human eye: Bruch membrane (B); choroid (C); retinal pigment epithelium (RPE); and retinal rod cells (R). The scale bar is 2um.

Magnification is the process of enlarging something only in appearance, not in physical size. This enlargement is quantified by a calculated number also called “magnification. ” The term magnification is often confused with the term “resolution,” which describes the ability of an imaging system to show detail in the object that is being imaged. While high magnification without high resolution may make very small microbes visible, it will not allow the observer to distinguish*between* microbes or sub-cellular parts of a microbe. In reality, therefore, microbiologists depend more on resolution, as they want to be able to determine differences between microbes or parts of microbes. However, to be able to distinguish between two objects under a microscope, a viewer must first magnify to a point at which resolution becomes relevant.

Resolution depends on the distance between two distinguishable radiating points. A microscopic imaging system may have many individual components, including a lens and recording and display components. Each of these contributes to the optical resolution of the system, as will the environment in which the imaging is performed. Real optical systems are complex, and practical difficulties often increase the distance between distinguishable point sources.

At very high magnifications with transmitted light, point objects are seen as fuzzy discs surrounded by diffraction rings. These are called Airy disks. The resolving power of a microscope is taken as the ability to distinguish between two closely spaced Airy disks (or, in other words, the ability of the microscope to distinctly reveal adjacent structural detail). It is this effect of diffraction that limits a microscope’s ability to resolve fine details. The extent and magnitude of the diffraction patterns are affected by the wavelength of light (λ), the refractive materials used to manufacture the objective lens, and the numerical aperture (NA) of the objective lens. There is therefore a finite limit beyond which it is impossible to resolve separate points in the objective field. This is known as the diffraction limit.

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SECTION OVERVIEW

3.2: Other Types of Microscopy

Topic hierarchy

3.2A: Microscopy

3.2B: General Staining Methods

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3.2A: Microscopy

Learning Objectives

- Compare and contrast light and electron microscopy.

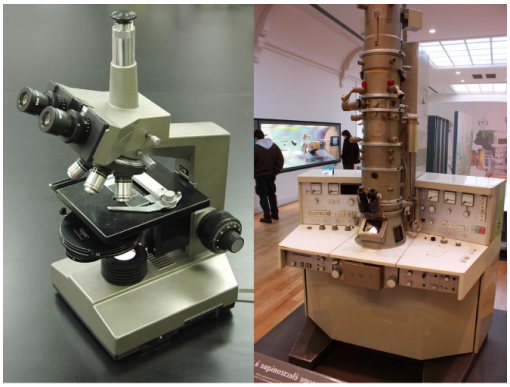
Cells vary in size. With few exceptions, individual cells cannot be seen with the naked eye, so scientists use microscopes (micro- = “small”; -scope = “to look at”) to study them. A microscope is an instrument that magnifies an object. Most photographs of cells are taken with a microscope; these images can also be called micrographs.

The optics of a microscope’s lenses change the orientation of the image that the user sees. A specimen that is right-side up and facing right on the microscope slide will appear upside-down and facing left when viewed through a microscope, and vice versa. Similarly, if the slide is moved left while looking through the microscope, it will appear to move right, and if moved down, it will seem to move up. This occurs because microscopes use two sets of lenses to magnify the image. Because of the manner by which light travels through the lenses, this system of two lenses produces an inverted image (binocular, or dissecting microscopes, work in a similar manner, but they include an additional magnification system that makes the final image appear to be upright).

Light Microscopes

To give you a sense of cell size, a typical human red blood cell is about eight millionths of a meter or eight micrometers (abbreviated as eight µm) in diameter; the head of a pin of is about two thousandths of a meter (two mm) in diameter. That means about 250 red blood cells could fit on the head of a pin.

Most student microscopes are classified as light microscopes. Visible light passes and is bent through the lens system to enable the user to see the specimen. Light microscopes are advantageous for viewing living organisms, but since individual cells are generally transparent, their components are not distinguishable unless they are colored with special stains. Staining, however, usually kills the cells.



(a) (b)

Figure: **Light and Electron Microscopes**: (a) Most light microscopes used in a college biology lab can magnify cells up to approximately 400 times and have a resolution of about 200 nanometers. (b) Electron microscopes provide a much higher magnification, 100,000x, and a have a resolution of 50 picometers.

Light microscopes, commonly used in undergraduate college laboratories, magnify up to approximately 400 times. Two parameters that are important in microscopy are magnification and resolving power. Magnification is the process of enlarging an object in appearance. Resolving power is the ability of a microscope to distinguish two adjacent structures as separate: the higher the resolution, the better the clarity and detail of the image. When oil immersion lenses are used for the study of small objects, magnification is usually increased to 1,000 times. In order to gain a better understanding of cellular structure and function, scientists typically use electron microscopes.

Electron Microscopes

In contrast to light microscopes, electron microscopes use a beam of electrons instead of a beam of light. Not only does this allow for higher magnification and, thus, more detail, it also provides higher resolving power. The method used to prepare the specimen for viewing with an electron microscope kills the specimen. Electrons have short wavelengths (shorter than photons) that move best in a vacuum, so living cells cannot be viewed with an electron microscope.

In a scanning electron microscope, a beam of electrons moves back and forth across a cell's surface, creating details of cell surface characteristics. In a transmission electron microscope, the electron beam penetrates the cell and provides details of a cell's internal structures. As you might imagine, electron microscopes are significantly more bulky and expensive than light microscopes.

Key Points

- Light microscopes allow for magnification of an object approximately up to 400-1000 times depending on whether the high power or oil immersion objective is used.
- Light microscopes use visible light which passes and bends through the lens system.
- Electron microscopes use a beam of electrons, opposed to visible light, for magnification.
- Electron microscopes allow for higher magnification in comparison to a light microscope thus, allowing for visualization of cell internal structures.

Key Terms

- **resolution**: The degree of fineness with which an image can be recorded or produced, often expressed as the number of pixels per unit of length (typically an inch).
- **electron**: The subatomic particle having a negative charge and orbiting the nucleus; the flow of electrons in a conductor constitutes electricity.

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3.2B: General Staining Methods

Learning Objectives

- Compare and contrast in vitro and in vivo staining

Staining is a technique used in microscopy to enhance contrast in a microscopic image. Stains and dyes are frequently used to highlight structures in microbes for viewing, often with the aid of different microscopes. Stains may be used to define and examine different types of microbes, various stages of cellular life (e.g., the mitotic cycle), and even organelles within individual cells (e.g., mitochondria or chloroplasts).

In-vivo staining is the process of dyeing living tissue — *in vivo* means "in life" (as contrasted to *in-vitro* staining). When a certain cell or structure takes on contrasting color(s), its form (morphology) or position within a cell or tissue can be readily seen and studied. The usual purpose is to reveal cytological details that might otherwise not be apparent; however, staining can also reveal where certain chemicals or specific chemical reactions are taking place within cells. *In-vitro* staining involves coloring cells or structures that have been removed from their biological context. Certain stains are often combined to reveal more details and features than a single stain could reveal alone, and a counterstain is a stain that increases visibility of cells or structures when the principal stain is not sufficient. Scientists and physicians can combine staining with specific protocols for fixation and sample preparation and can use these standard techniques as consistent, repeatable diagnostic tools.

There are an incredible number of stains that can be used in a variety of different methods. What follows here are some common aspects of the process of preparing for *in-vitro* staining.

- Fixation: This can itself consist of several steps. Fixation aims to preserve the shape of the cells (in this case, microbes) as much as possible. Sometimes heat fixation is used to kill, adhere, and alter the cells so they will accept stains. Most chemical fixatives generate chemical bonds between proteins and other substances within the sample, increasing their rigidity. Common fixatives include formaldehyde, ethanol, methanol, and picric acid.
- Permeabilization: This involves treatment of the cells with (usually) a mild surfactant. This treatment dissolves cell membranes, allowing larger dye molecules to enter the cell's interior.
- Mounting: This step usually involves attaching the samples to a glass microscope slide for observation and analysis. In some cases, cells may be grown directly on a slide. For samples of loose cells the sample can be directly applied to a slide.

At its simplest, the actual staining process may involve immersing the sample (before or after fixation and mounting) in dye solution, followed by rinsing and observation. Many dyes, however, require the use of a mordant — a chemical compound that reacts with the stain to form an insoluble colored precipitate. When the excess dye solution is washed away, the mordanted stain remains. There is an incredible array of stains that can be used at this step, from those that stain specific microbial types (see the figure below) to those that highlight sub-compartments or organelles of a cell, such as the nucleus or endoplasmic reticulum. Alternatively, negative staining can be employed. This is a simple staining method for bacteria, performed by smearing the cells onto the slide and then applying nigrosin (a black synthetic dye) or Indian ink (an aqueous suspension of carbon particles). After drying, the microorganisms may be viewed in bright field microscopy as lighter inclusions contrast well against the dark environment surrounding them

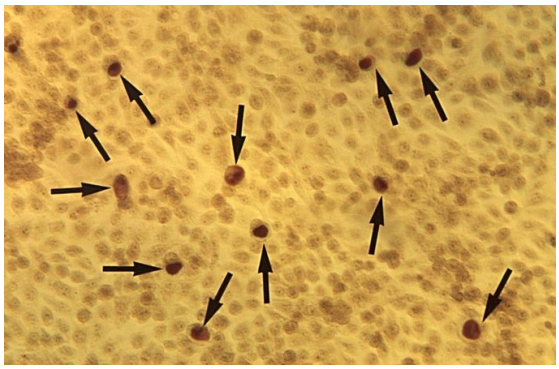

Figure: **Chlamydia Stain**: Cells of the bacterial pathogen chlamydia (indicated by arrows) are highlighted by a stain called "geimsa. "

Live, *in-vivo* staining microscopy shares many of these steps, with the exception of fixation, which invariably kills the microbe to be examined.

Key Points

- In-vivo staining, which visualizes cells that are alive, and in-vitro staining, which visualizes fixed cells, both have important uses.
- There is a vast array of stains that can be used on microbes that can highlight almost any characteristic of a cell, even organelles within a cell.
- Staining protocols can be complex, but they share some basic steps: preparation, fixation, staining, and mounting.

Key Terms

- **surfactant**: a surface active agent, or wetting agent, capable of reducing the surface tension of a liquid; typically organic compounds having a hydrophilic “head” and a hydrophobic “tail”
- **organelle**: a specialized structure found inside cells that carries out a specific life process (e.g., ribosomes, vacuoles)

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SECTION OVERVIEW

3.3: Other Types of Microscopy

Topic hierarchy

3.3A: Dark-Field Microscopy

3.3B: Phase-Contrast Microscopy

3.3C: Interference Microscopy

3.3D: Fluorescence Microscopy

3.3E: Confocal Micropscopy

3.3F: Electron Microscopy

3.3G: Scanned-Probe Microscopy

3.3H: X-Ray Diffraction Analysis

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3.3A: Dark-Field Microscopy

Learning Objectives

- Generalize the process of dark-field microscopy

Radiance Against a Dark Background

Dark-field microscopy is ideally used to illuminate unstained samples causing them to appear brightly lit against a dark background. This type of microscope contains a special condenser that scatters light and causes it to reflect off the specimen at an angle. Rather than illuminating the sample with a filled cone of light, the condenser is designed to form a hollow cone of light. The light at the apex of the cone is focused at the plane of the specimen; as this light moves past the specimen plane it spreads again into a hollow cone. The objective lens sits in the dark hollow of this cone; although the light travels around and past the objective lens, no rays enter it.



Figure: **Visualization of live bacteria**: Spirochetes bacteria observed under dark field microscopy.

The entire field appears dark when there is no sample on the microscope stage; thus the name dark-field microscopy. When a sample is on the stage, the light at the apex of the cone strikes it. The rays scattered by the sample and captured in the objective lens thus make the image.

Samples observed under dark-field microscopy should be carefully prepared since dust and other particles also scatter the light and are easily detected. Glass slides need to be thoroughly cleaned of extraneous dust and dirt. It may be necessary to filter sample media (agar, water, saline) to exclude confusing contaminants. Sample materials need to be spread thinly; too much material on the slide creates many overlapping layers and edges, making it difficult to interpret structures.

Dark-field microscopy has many applications in microbiology. It allows the visualization of live bacteria, and distinguishes some structure (rods, curved rods, spirals, or cocci) and movement.

Key Points

- In dark-field microscopy, the light reaches the specimen from an angle with the help of an opaque disk.
- The specimen appears lit up agains a dark background.
- Dark-field microscopy is most useful for extremely small living organisms that are invisible in the light microscope.

Key Terms

- **condenser**: A lens (or combination of lenses) designed to gather light and focus it onto a specimen or part of a mechanism.

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3.3B: Phase-Contrast Microscopy

Phase-contrast microscopy visualizes differences in the refractive indexes of different parts of a specimen relative to unaltered light.

Learning Objectives

- Describe the mechanics, advantages, and disadvantages of phase-contrast microscopy

Key Points

- A phase-contrast microscope splits a beam of light into 2 types of light, direct and refracted (reflected) and brings them together to form an image of the specimen.
- Where the lights are “in-phase” the image is brighter, where the lights are “out of phase” the image is darker, and by amplifying these differences in the light, it enhances contrast.
- Phase-contrast microscopy allows for the detailed observation of living organisms, especially the internal structures.

Key Terms

- **refractive index**: the ratio of the speed of light in air or vacuum to that in another medium.

Phase-contrast microscopy is a method of manipulating light paths through the use of strategically placed rings in order to illuminate transparent objects. Dutch physicist Fritz Zernike developed the technique in the 1930s; for his efforts he was awarded the Nobel Prize in 1953.

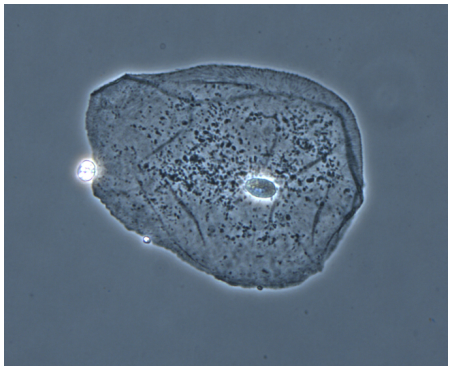

Figure: **Phase-contrast microscopy**: Phase-contrast image of a cheek epithelial cell.

In phase-contrast microscopy, parallel beams of light are passed through objects of different densities. The microscope contains special condensers that throw light “out of phase” causing it to pass through the object at different speeds. Internal details and organelles of live, unstained organisms (e.g. mitochondria, lysosomes, and the Golgi body) can be seen clearly with this microscope.

A phase ring in condenser allows a cylinder of light to pass through it while still in phase. Unaltered light hits the phase ring in the lens and is excluded. Light that is slightly altered by passing through a different refractive index is allowed to pass through. Light passing through cellular structures, such as chromosomes or mitochondria is retarded because they have a higher refractive index than the surrounding medium. Elements of lower refractive index advance the wave. Much of the background light is removed and light that constructively or destructively interfered is let through with enhanced contrast.

Phase-contrast microscopy allows the visualization of living cells in their natural state with high contrast and high resolution. This tool works best with a thin specimen and is not ideal for a thick specimen. Phase-contrast images have a characteristic grey background with light and dark features found across the sample. One disadvantage of phase-contrast microscopy is halo formation called halo-light ring.

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3.3C: Interference Microscopy

LEARNING OBJECTIVES

- Describe the principles and different types of interference microscopy

Stereo Light Source

Interference microscopy uses a prism to split light into two slightly diverging beams that then pass through the specimen. It is thus based on measuring the differences in refractive index upon recombining the two beams. Interference occurs when a light beam is retarded or advanced relative to the other.

There are three types of interference microscopy: classical, differential contrast, and fluorescence contrast. Since its introduction in the late 1960s differential interference contrast microscopy (DIC) has been popular in biomedical research because it produces high-resolution images of fine structures by enhancing the contrasted interfaces. The image produced is of a thin optical section and appears three-dimensional, with a shadow around it. This creates a contrast across the specimen that is bright on one side and darker on the other.

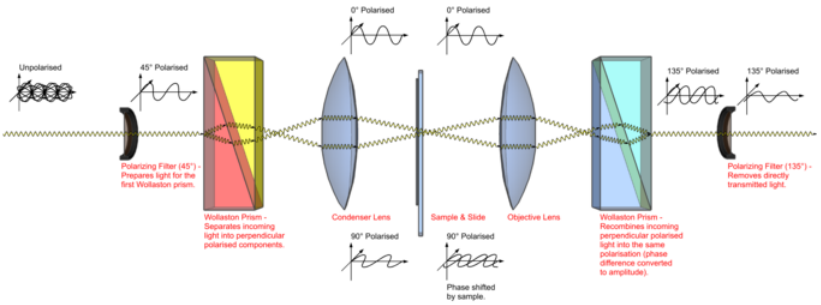

Figure: **Path of light in differential interference contrast microscopy (DIC)**: Two parallel light beams pass through the specimen and combine to produce an image.

The Interference Microscope

The microscope is a bright field light microscope with the addition of the following elements: a polarizer between the light source and the condenser, a DIC beam-splitting prism, a DIC beam-combining prism, and an analyzer. Manipulating the prism changes the beam separation, which alters the contrast of the image. When the two beams pass through the same material across the specimen they produce no interference. When the two beams pass through different material across the specimen such as on the edges, they produce alteration when combined.

Fluorescence differential interference contrast (FLIC) microscopy was developed by combining fluorescence microscopy with DIC to minimize the effects of photobleaching on fluorochromes bound to the stained specimen. The same microscope is equipped to simulataneously image a specimen using DIC and fluorescence illumination.

Key Points

- Interference microscopy is superior to phase-contrast microscopy in its ability to eliminate halos and extra light.
- In differential interference contrast microscopy (DIC), the optical path difference is determined by the product of the refractive index difference (between the specimen and its surrounding medium) and the thickness traversed by a light beam between two points on the optical path.
- Images produced by DIC have a distinctive shadow-cast appearance.

Key Terms

- **photobleaching**: The destruction of a photochemical fluorescence by high-intensity light
- **fluorochrome**: Any of various fluorescent dyes used to stain biological material before microscopic examination

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3.3D: Fluorescence Microscopy

Learning Objectives

- Describe the techniques, advantages, and disadvantages of fluorescence microscopy

The fluorescent microscope uses a high-pressure mercury, halogen, or xenon vapor lamp that emits a shorter wavelength than that emitted by traditional brightfield microscopy. These light sources produce ultraviolet light. When ultraviolet light hits an object, it excites the electrons of the object, and they give off light in various shades of color. Since ultraviolet light is used a larger amount of information can be gathered; thus, the resolution of the object increases.

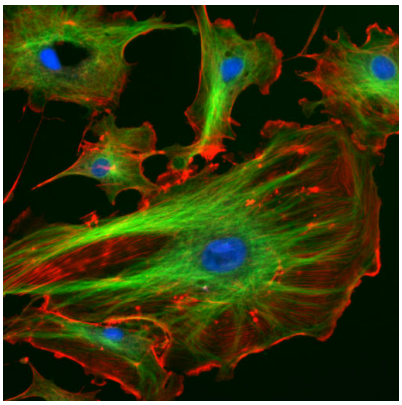

Figure: **Fluorescent cells.**: Fixed endothelial cells stained with fluorescent dyes. Nuclei are stained blue with DAPI, microtubules are stained green by an antibody bound to FITC and actin filaments are labelled red with phalloidin bound to TRITC.

Fluorescent-Antibody Technique and Dyes

This laboratory technique employs fluorescent dyes chemically linked to antibodies to help identify unknown microorganisms. This method uses the specificity of an antibody to its antigen to deliver a fluorescent dye to a target molecule. A filter is used to block the heat generated from the lamp and to match the fluorescent dye labeling the specimen. An additional barrier filter between the objective and the detector can filter out the remaining excitation light from fluorescent light.

Fluorescent dyes—molecules that absorb light of one wavelength and then re-emit it at a longer visible wavelength—can be used alone or in combination to gain specificity of the stained structure being visualized. The light emitted from the fluorophore is magnified through traditional objectives and ocular lenses. Staining organisms with these special dyes reduces the non-specific autofluorescence that some organisms can emit. Cells or organisms stained with fluorochromes appear colored against a dark background when fixed on a glass slide. Fluorescence microscopy does not allow examination of live microorganisms as it requires them to be fixed and permeabilized for the antibody to penetrate inside the cells.

Key Points

- In fluorescence microscopy, specimens are first stained with fluorochromes and then viewed through a compound microscope by using an ultraviolet (or near-ultraviolet) light source.
- Microorganisms appear as bright objects against a dark background.
- Fluorescence microscopy is used primarily in a procedure called fluorescent- antibody (FA) technique, or immunofluorescence.

Key Terms

- **autofluorescence**: Self-induced fluorescence
- **halogen**: any element of group 7, i.e. fluorine, chlorine, bromine, iodine and astatine, which form a salt by direct union with a metal

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3.3E: Confocal Micropscopy

Learning Objectives

- Compare and contrast confocal and fluorescence microscopy

Confocal microscopy is a non-invasive fluorescent imaging technique that uses lasers of various colors to scan across a specimen with the aid of scanning mirrors. The point of illumination is brought to focus in the specimen by the objective lens. The scanning process uses a device that is under computer control. The sequences of points of light from the specimen are detected by a photomultiplier tube through a pinhole. The output is built into an image and transferred onto a digital computer screen for further analysis. The technique employs optical sectioning to take serial slices of the image. The slices are then stacked (Z-stack) to reconstruct the three-dimensional image of the biological sample. Optical sectioning is useful in determining cellular localization of targets. The biological sample to be studied is stained with antibodies chemically bound to fluorescent dyes similar to the method employed in fluorescence microscopy. Unlike in conventional fluorescence microscopy where the fluorescence is emitted along the entire illuminated cone creating a hazy image, in confocal microscopy the pinhole is added to allow passing of light that comes from a specific focal point on the sample and not the other. The light detected creates an image that is in focus with the original sample. Confocal microscopy has multiple applications in microbiology such as the study of biofilms and antibiotic-resistant strains of bacteria. Development of modern confocal microscopes has been accelerated by new advances in computer and storage technology, laser systems, detectors, interference filters, and fluorophores for highly specific targets.

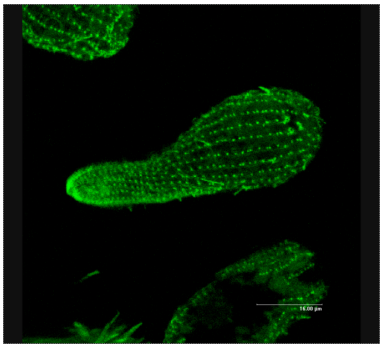

Figure: ***Confocal Microscopy****: Tetrahymena cell, visualized using GFP-labeled anti-beta tubulin antibodies under confocal microscopy.*

Key Points

- Confocal microscopy requires immunoflurescence staining of biological samples.
- Confocal microscopy serves to control depth of field, eliminate background, and collect optical sections.
- The use of confocal microscopy has expanded to study both fixed and live cells with the ability to quantify targets.

Key Terms

- **photomultiplier tube**: A vacuum tube that detects ultraviolet, visible, and near infrared light and multiplies it 100 million times.

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3.3F: Electron Microscopy

Learning Objectives

- Describe the technique employed for electron microscopy, distinguishing between different types

Electron microscopy uses a beam of electrons as an energy source. An electron beam has an exceptionally short wavelength and can hit most objects in its path, increasing the resolution of the final image captured. The electron beam is designed to travel in a vacuum to limit interference by air molecules. Magnets are used to focus the electrons on the object viewed.

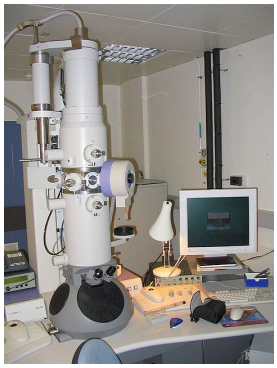

Figure: ***Electron microscope**: A modern electron microscope*

There are two types of electron microscopes. The more traditional form is the transmission electron microscope (TEM). To use this instrument, ultra-thin slices of microorganisms or viruses are placed on a wire grid and then stained with gold or palladium before viewing, to create contrast. The densely coated parts of the specimen deflect the electron beam and both dark and light areas show up on the image. TEM can project images in a much higher resolution—up to the atomic level of thinner objects.

The second and most contemporary form is the scanning electron microscope (SEM). It allows the visualization of microorganisms in three dimensions as the electrons are reflected when passed over the specimen. The same gold or palladium staining is employed.

Electron microscopy has multiple applications. It is ideal to:

- explore the in vivo molecular mechanisms of disease;
- visualize the three dimensional architecture of tissues and cells;
- determine the conformation of flexible protein structures and complexes;
- observe individual viruses and macromolecular complexes in their natural biological context.

Sample preparation can be critical to generate a successful image because the choice of reagents and methods used to process a sample largely depends on the nature of the sample and the analysis required.

Key Points

- A beam of electrons, instead of light, is used with an electron microscope.
- Electron microscopes have a greater magnification because the wavelengths of electrons are much smaller than those of visible light (0.005nm as opposed to 500nm respectively–one hundred thousand times smaller).
- There are two types of electron microscopes, scanning and transmission.
- The best compound light microscopes can magnify 2000x, electron microscopes can magnify up to 100,000x.

Key Terms

- **electron beam**: a stream of electrons observed in vacuum tubes.

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3.3G: Scanned-Probe Microscopy

Learning Objectives

- Describe the different types of scanning probe techniques and their advantages over other types of microscopy

3-D Images

Scanned-probe microscopy (SPM) produces highly magnified and three-dimensional-shaped images of specimens in real time. SPM employs a delicate probe to scan the surface of the specimen, eliminating the limitations that are found in electron and light microscopy. SPM covers several related technologies for imaging and measuring surfaces on a fine scale, down to the level of molecules and groups of atoms.

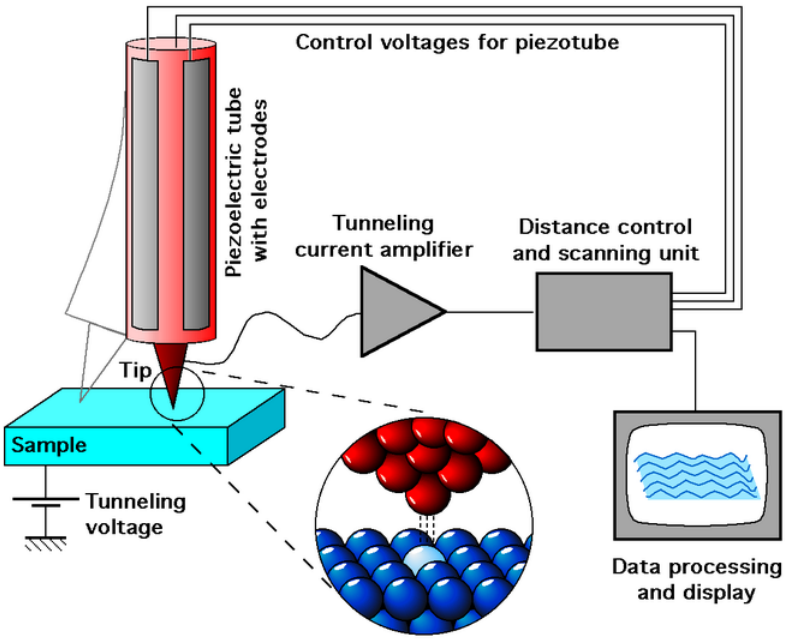

Figure: **Scanning tunneling microscopy**: Schematic diagram of a scanning tunneling microscope.

A scan may cover a distance of over 100 micrometers in the x and y directions and 4 micrometers in the z direction. SPM technologies share the concept of scanning a sharp probe tip with a small radius of curvature across the object surface. The tip is mounted on a flexible cantilever, allowing the tip to follow the surface profile. When the tip moves in proximity to the investigated object, forces of interaction between the tip and the surface influence the movement of the cantilever. Selective sensors detect these movements. Various interactions can be studied depending on the mechanics of the probe.

There are three common scanning probe techniques: *atomic force microscopy* (AFM) measures the *interaction force* between the tip and surface. The tip may be dragged across the surface, or may vibrate as it moves. The interaction force will depend on the nature of the sample, the probe tip and the distance between them. S*canning tunneling microscopy* (STM) measures a *weak electrical current* flowing between tip and sample as they are held apart. *Near-field scanning optical microscopy* (NSOM) scans a very *small light source* very close to the sample. Detection of this light energy forms the image.

Key Points

- Scanned-probe microscopy has enabled researchers to create images of surfaces at the nanometer scale with a probe.
- The probe has an extremely sharp tip that interacts with the surface of the specimen.
- There are several variations of scanned-probe microscopy of which atomic force microscopy, scanning tunneling microscopy, and near-field scanning optical microscopy are most commonly used.

Key Terms

- **micrometer**: An SI/MKS unit of measure, the length of one one-millionth of a meter. Symbols: µm, um, rm

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3.3H: X-Ray Diffraction Analysis

Learning Objectives

- Summarize the methods used for x-ray diffraction analysis and the contributions they have made to science

X-ray diffraction (XRD) is a tool for characterizing the arrangement of atoms in crystals and the distances between crystal faces. The technique reveals detailed information about the chemical composition, crystallography, and microstructure of all types of natural and manufactured materials, which is key in understanding the properties of the material being studied.

Since many materials can form crystals—such as salts, metals, minerals, semiconductors, as well as various inorganic, organic, and biological molecules —X-ray crystallography has been fundamental in the development of many scientific fields. The method determined the size of atoms, the lengths and types of chemical bonds, and the atomic-scale differences among various materials, especially minerals and alloys. The method also revealed the structure and function of many biological molecules, including vitamins, drugs, proteins, and nucleic acids such as DNA.

Samples are commonly analyzed in a crystal form. X-ray diffraction is caused by constructive interference of x-ray waves that reflect off internal crystal planes. A thin film or layer of powder is fixed in the path of monochromatic x-rays. A detector measures x-rays from the sample over a range of angles. The powder consists of tiny crystals randomly oriented. At certain angles of the sensor, populations of crystals have the correct angle so that Bragg's equation is satisfied for one of the crystal planes, resulting in a spike in X-rays.

The output graph displays x-ray intensity over 2 theta, the angle of the detector. The data generated with this technique requires extensive mathematical analysis that is now made easier by available computer algorithms. The analysis consists of indexing, merging, and phasing variations in electron density. It begins with the identification of molecules using the international center for diffraction database (ICDD). This is an organization dedicated to collecting, editing, publishing, and distributing powder diffraction data for the identification of crystalline materials. Further analysis involves structure refinement and quantitative phase using the general structure analysis system (GSAS), which ultimately leads to the identification of the amorphous or crystalline phase of a matter and helps construct its three dimensional atomic model.

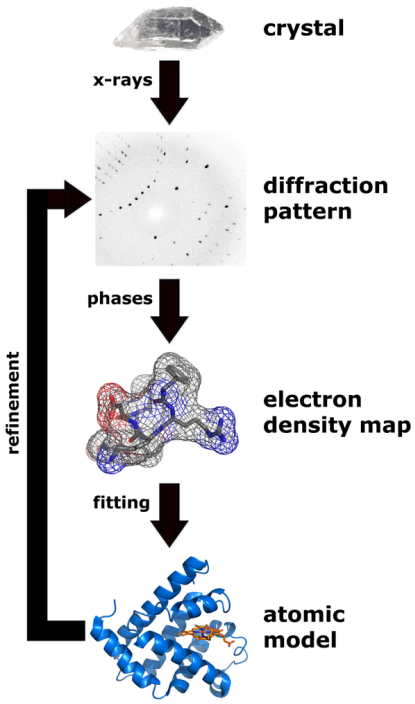

Figure: ***Structure determination by X-ray crystallography****: X-ray diffraction analysis workflow. In an X-ray diffraction measurement, a crystal is mounted on a goniometer and gradually rotated while being bombarded with X-rays, producing a diffraction pattern of regularly spaced spots known as reflections. The two-dimensional images taken at different rotations are converted into a three-dimensional model of the density of electrons within the crystal using the mathematical method of Fourier transforms, combined with chemical data known for the sample.*

Key Points

- X-ray diffraction utilizes x-ray beams targeted to hit crystallized matter and generates a diffraction pattern.
- Data collected using this method undergo a systematic analytical process that employes mathematical models and computer algorithms to obtain the final 3D atom model of a matter.
- X-ray diffraction analysis identifies composition and chemical bonds between atoms of crystal, liquid, powder, or amorphous samples.

Key Terms

- **Bragg's equation**: Gives the angles for coherent and incoherent scattering from a crystal lattice.
- **crystallography**: The experimental science of determining the arrangement of atoms in solids.

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CHAPTER OVERVIEW

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Thumbnail: A 3D rendering of an animal cell cut in half. (CC -BY-SA 4.0; Zaldua I., Equisoain J.J., Zabalza A., Gonzalez E.M., Marzo A., Public University of Navarre).

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SECTION OVERVIEW

4.1: Overview of Prokaryotic and Eukaryotic Cells

Topic hierarchy

4.1A: Characteristics of Prokaryotic Cells

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4.1A: Characteristics of Prokaryotic Cells

A prokaryote is a simple, unicellular organism that lacks an organized nucleus or other membrane-bound organelle.

Learning Objectives

- Describe the structure of prokaryotic cells

Key Points

- Prokaryotes lack an organized nucleus and other membrane-bound organelles.
- Prokaryotic DNA is found in a central part of the cell called the nucleoid.
- The cell wall of a prokaryote acts as an extra layer of protection, helps maintain cell shape, and prevents dehydration.
- Prokaryotic cell size ranges from 0.1 to 5.0 μm in diameter.
- The small size of prokaryotes allows quick entry and diffusion of ions and molecules to other parts of the cell while also allowing fast removal of waste products out of the cell.

Key Terms

- **eukaryotic**: Having complex cells in which the genetic material is organized into membrane-bound nuclei.
- **prokaryotic**: Of cells, lacking a nucleus.
- **nucleoid**: the irregularly-shaped region within a prokaryote cell where the genetic material is localized

Components of Prokaryotic Cells

All cells share four common components:

1. a plasma membrane: an outer covering that separates the cell's interior from its surrounding environment.
2. cytoplasm: a jelly-like cytosol within the cell in which other cellular components are found
3. DNA: the genetic material of the cell
4. ribosomes: where protein synthesis occurs

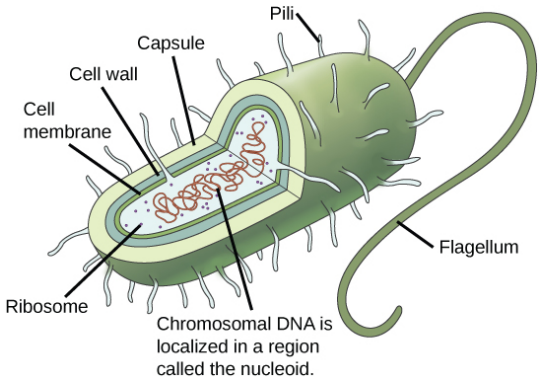

Figure: **General Structure of a Prokaryotic Cell**: This figure shows the generalized structure of a prokaryotic cell.All prokaryotes have chromosomal DNA localized in a nucleoid, ribosomes, a cell membrane, and a cell wall.The other structures shown are present in some, but not all, bacteria.

However, prokaryotes differ from eukaryotic cells in several ways.

A prokaryote is a simple, single-celled (unicellular) organism that lacks an organized nucleus or any other membrane-bound organelle. We will shortly come to see that this is significantly different in eukaryotes. Prokaryotic DNA is found in a central part of the cell: the nucleoid.

Most prokaryotes have a peptidoglycan cell wall and many have a polysaccharide capsule. The cell wall acts as an extra layer of protection, helps the cell maintain its shape, and prevents dehydration. The capsule enables the cell to attach to surfaces in its environment. Some prokaryotes have flagella, pili, or fimbriae. Flagella are used for locomotion. Pili are used to exchange genetic material during a type of reproduction called conjugation. Fimbriae are used by bacteria to attach to a host cell.

Cell Size

At 0.1 to 5.0 μm in diameter, prokaryotic cells are significantly smaller than eukaryotic cells, which have diameters ranging from 10 to 100 μm. The small size of prokaryotes allows ions and organic molecules that enter them to quickly diffuse to other parts of the cell. Similarly, any wastes produced within a prokaryotic cell can quickly diffuse out. This is not the case in eukaryotic cells, which have developed different structural adaptations to enhance intracellular transport.

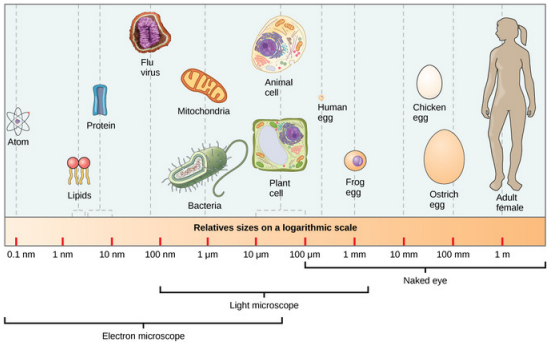

Figure: **Microbial Size**: This figure shows relative sizes of microbes on a logarithmic scale (recall that each unit of increase in a logarithmic scale represents a 10-fold increase in the quantity being measured).

Small size, in general, is necessary for all cells, whether prokaryotic or eukaryotic. Let's examine why that is so. First, we'll consider the area and volume of a typical cell. Not all cells are spherical in shape, but most tend to approximate a sphere. You may remember from your high school geometry course that the formula for the surface area of a sphere is $4\pi r^2$, while the formula for its volume is $4/3\pi r^3$. Thus, as the radius of a cell increases, its surface area increases as the square of its radius, but its volume increases as the cube of its radius (much more rapidly). Therefore, as a cell increases in size, its surface area-to-volume ratio decreases. This same principle would apply if the cell had the shape of a cube. If the cell grows too large, the plasma membrane will not have sufficient surface area to support the rate of diffusion required for the increased volume. In other words, as a cell grows, it becomes less efficient. One way to become more efficient is to divide; another way is to develop organelles that perform specific tasks. These adaptations led to the development of more sophisticated cells called eukaryotic cells.

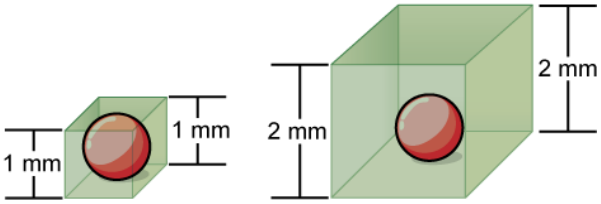

Figure: **Cell Surface Size**: Notice that as a cell increases in size, its surface area-to-volume ratio decreases.When there is insufficient surface area to support a cell's increasing volume, a cell will either divide or die.The cell on the left has a volume of 1 mm3 and a surface area of 6 mm2, with a surface area-to-volume ratio of 6 to 1, whereas the cell on the right has a volume of 8 mm3 and a surface area of 24 mm2, with a surface area-to-volume ratio of 3 to 1.

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SECTION OVERVIEW

4.2: The Cytoplasmic Membrane of Prokaryotic and Eukaryotic Cells

Topic hierarchy

4.2A: Components of Plasma Membranes

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4.2A: Components of Plasma Membranes

The plasma membrane protects the cell from its external environment, mediates cellular transport, and transmits cellular signals.

Learning Objectives

- Describe the function and components of the plasma membrane

Key Points

- The principal components of the plasma membrane are lipids (phospholipids and cholesterol), proteins, and carbohydrates.
- The plasma membrane protects intracellular components from the extracellular environment.
- The plasma membrane mediates cellular processes by regulating the materials that enter and exit the cell.
- The plasma membrane carries markers that allow cells to recognize one another and can transmit signals to other cells via receptors.

Key Terms

- **plasma membrane**: The semipermeable barrier that surrounds the cytoplasm of a cell.
- **receptor**: A protein on a cell wall that binds with specific molecules so that they can be absorbed into the cell.

Structure of Plasma Membranes

The plasma membrane (also known as the cell membrane or cytoplasmic membrane) is a biological membrane that separates the interior of a cell from its outside environment.

The primary function of the plasma membrane is to protect the cell from its surroundings. Composed of a phospholipid bilayer with embedded proteins, the plasma membrane is selectively permeable to ions and organic molecules and regulates the movement of substances in and out of cells. Plasma membranes must be very flexible in order to allow certain cells, such as red blood cells and white blood cells, to change shape as they pass through narrow capillaries.

The plasma membrane also plays a role in anchoring the cytoskeleton to provide shape to the cell, and in attaching to the extracellular matrix and other cells to help group cells together to form tissues. The membrane also maintains the cell potential.

In short, if the cell is represented by a castle, the plasma membrane is the wall that provides structure for the buildings inside the wall, regulates which people leave and enter the castle, and conveys messages to and from neighboring castles. Just as a hole in the wall can be a disaster for the castle, a rupture in the plasma membrane causes the cell to lyse and die.

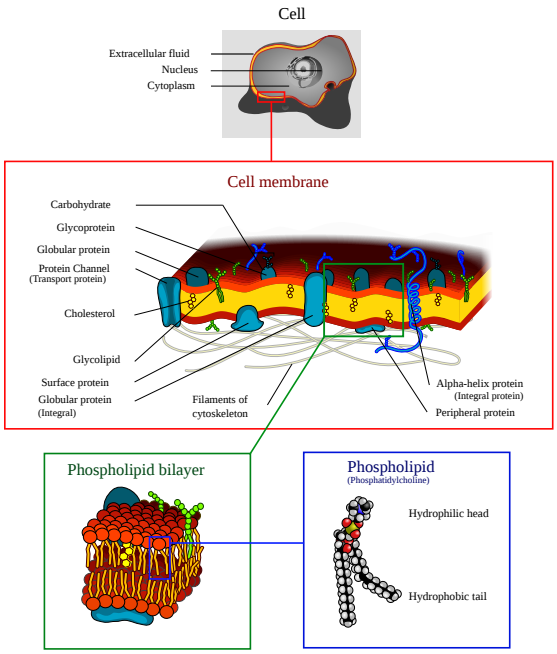

Figure: **The plasma membrane**: The plasma membrane is composed of phospholipids and proteins that provide a barrier between the external environment and the cell, regulate the transportation of molecules across the membrane, and communicate with other cells via protein receptors.

The Plasma Membrane and Cellular Transport

The movement of a substance across the selectively permeable plasma membrane can be either "passive"—i.e., occurring without the input of cellular energy —or "active"—i.e., its transport requires the cell to expend energy.

The cell employs a number of transport mechanisms that involve biological membranes:

1. Passive osmosis and diffusion: transports gases (such as O_2 and CO_2)and other small molecules and ions
2. Transmembrane protein channels and transporters: transports small organic molecules such as sugars or amino acids
3. Endocytosis: transports large molecules (or even whole cells) by engulfing them
4. Exocytosis: removes or secretes substances such as hormones or enzymes

The Plasma Membrane and Cellular Signaling

Among the most sophisticated functions of the plasma membrane is its ability to transmit signals via complex proteins. These proteins can be receptors, which work as receivers of extracellular inputs and as activators of intracellular processes, or markers, which allow cells to recognize each other.

Membrane receptors provide extracellular attachment sites for effectors like hormones and growth factors, which then trigger intracellular responses. Some viruses, such as Human Immunodeficiency Virus (HIV), can hijack these receptors to gain entry into the cells, causing infections.

Membrane markers allow cells to recognize one another, which is vital for cellular signaling processes that influence tissue and organ formation during early development. This marking function also plays a later role in the "self"-versus-"non-self" distinction of the immune response. Marker proteins on human red blood cells, for example, determine blood type (A, B, AB, or O).

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SECTION OVERVIEW

4.3: Transport Across the Cell Membrane

Topic hierarchy

4.3A: Facilitated Transport

4.3B: Primary Active Transport

4.3C: ABC Transporters

4.3D: Siderophores

4.3E: Group Translocation

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4.3A: Facilitated Transport

Learning Objectives

- Explain why and how passive transport occurs

Facilitated transport is a type of passive transport. Unlike simple diffusion where materials pass through a membrane without the help of proteins, in facilitated transport, also called facilitated diffusion, materials diffuse across the plasma membrane with the help of membrane proteins. A concentration gradient exists that would allow these materials to diffuse into the cell without expending cellular energy. However, these materials are ions or polar molecules that are repelled by the hydrophobic parts of the cell membrane. Facilitated transport proteins shield these materials from the repulsive force of the membrane, allowing them to diffuse into the cell.

The material being transported is first attached to protein or glycoprotein receptors on the exterior surface of the plasma membrane. This allows the material that is needed by the cell to be removed from the extracellular fluid. The substances are then passed to specific integral proteins that facilitate their passage. Some of these integral proteins are collections of beta-pleated sheets that form a channel through the phospholipid bilayer. Others are carrier proteins which bind with the substance and aid its diffusion through the membrane.

Channels

The integral proteins involved in facilitated transport are collectively referred to as transport proteins; they function as either channels for the material or carriers. In both cases, they are transmembrane proteins. Channels are specific for the substance that is being transported. Channel proteins have hydrophilic domains exposed to the intracellular and extracellular fluids; they additionally have a hydrophilic channel through their core that provides a hydrated opening through the membrane layers. Passage through the channel allows polar compounds to avoid the nonpolar central layer of the plasma membrane that would otherwise slow or prevent their entry into the cell. Aquaporins are channel proteins that allow water to pass through the membrane at a very high rate.

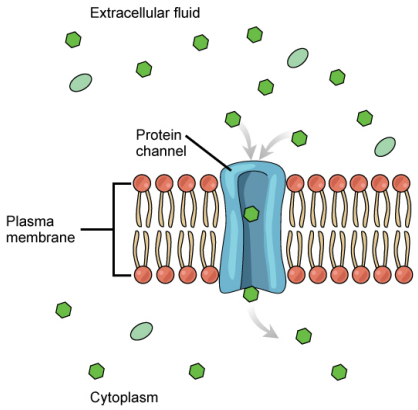

Figure: **Channel Proteins in Facilitated Transport**: Facilitated transport moves substances down their concentration gradients. They may cross the plasma membrane with the aid of channel proteins.

Channel proteins are either open at all times or they are “gated,” which controls the opening of the channel. The attachment of a particular ion to the channel protein may control the opening or other mechanisms or substances may be involved. In some tissues, sodium and chloride ions pass freely through open channels, whereas in other tissues, a gate must be opened to allow passage. An example of this occurs in the kidney, where both forms of channels are found in different parts of the renal tubules. Cells involved in the transmission of electrical impulses, such as nerve and muscle cells, have gated channels for sodium, potassium, and calcium in their membranes. Opening and closing of these channels changes the relative concentrations on opposing sides of the membrane of these ions, resulting in the facilitation of electrical transmission along membranes (in the case of nerve cells) or in muscle contraction (in the case of muscle cells).

Carrier Proteins

Another type of protein embedded in the plasma membrane is a carrier protein. This protein binds a substance and, in doing so, triggers a change of its own shape, moving the bound molecule from the outside of the cell to its interior; depending on the

gradient, the material may move in the opposite direction. Carrier proteins are typically specific for a single substance. This adds to the overall selectivity of the plasma membrane. The exact mechanism for the change of shape is poorly understood. Proteins can change shape when their hydrogen bonds are affected, but this may not fully explain this mechanism. Each carrier protein is specific to one substance, and there are a finite number of these proteins in any membrane. This can cause problems in transporting enough of the material for the cell to function properly.

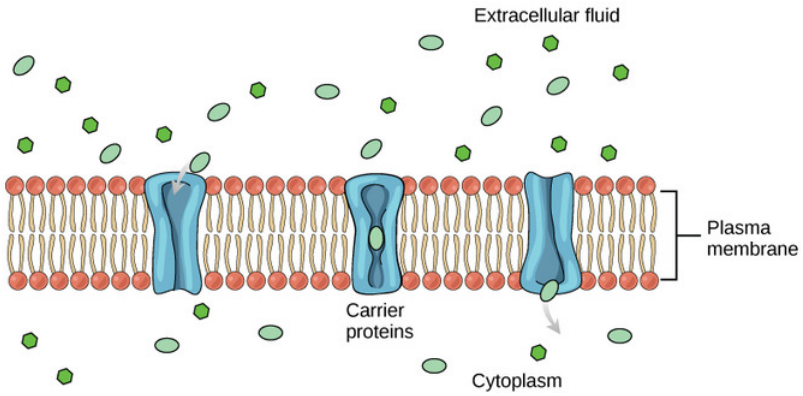

Figure: ***Carrier Proteins****: Some substances are able to move down their concentration gradient across the plasma membrane with the aid of carrier proteins. Carrier proteins change shape as they move molecules across the membrane.*

An example of this process occurs in the kidney. Glucose, water, salts, ions, and amino acids needed by the body are filtered in one part of the kidney. This filtrate, which includes glucose, is then reabsorbed in another part of the kidney. Because there are only a finite number of carrier proteins for glucose, if more glucose is present than the proteins can handle, the excess is not transported; it is excreted from the body in the urine. In a diabetic individual, this is described as "spilling glucose into the urine." A different group of carrier proteins called glucose transport proteins, or GLUTs, are involved in transporting glucose and other hexose sugars through plasma membranes within the body.

Channel and carrier proteins transport material at different rates. Channel proteins transport much more quickly than do carrier proteins. Channel proteins facilitate diffusion at a rate of tens of millions of molecules per second, whereas carrier proteins work at a rate of a thousand to a million molecules per second.

Key Points

- A concentration gradient exists that would allow ions and polar molecules to diffuse into the cell, but these materials are repelled by the hydrophobic parts of the cell membrane.
- Facilitated diffusion uses integral membrane proteins to move polar or charged substances across the hydrophobic regions of the membrane.
- Channel proteins can aid in the facilitated diffusion of substances by forming a hydrophilic passage through the plasma membrane through which polar and charged substances can pass.
- Channel proteins can be open at all times, constantly allowing a particular substance into or out of the cell, depending on the concentration gradient; or they can be gated and can only be opened by a particular biological signal.
- Carrier proteins aid in facilitated diffusion by binding a particular substance, then altering their shape to bring that substance into or out of the cell.

Key Terms

- **facilitated diffusion**: The spontaneous passage of molecules or ions across a biological membrane passing through specific transmembrane integral proteins.
- **membrane protein**: Proteins that are attached to, or associated with the membrane of a cell or an organelle.

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4.3B: Primary Active Transport

Learning Objectives

Describe how a cell moves sodium and potassium out of and into the cell against its electrochemical gradient

The sodium-potassium pump maintains the electrochemical gradient of living cells by moving sodium in and potassium out of the cell. The primary active transport that functions with the active transport of sodium and potassium allows secondary active transport to occur. The secondary transport method is still considered active because it depends on the use of energy as does primary transport.

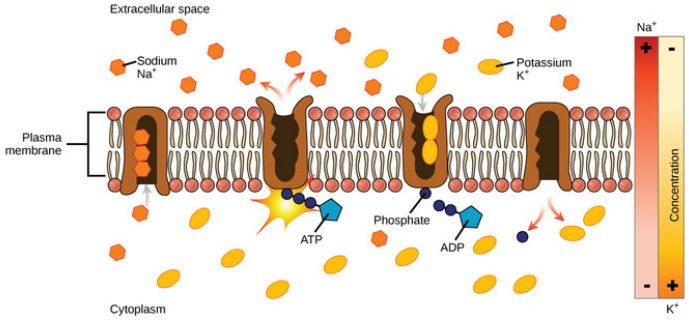

Figure: **Active Transport of Sodium and Potassium**: Primary active transport moves ions across a membrane, creating an electrochemical gradient (electrogenic transport).

One of the most important pumps in animals cells is the sodium-potassium pump (Na^+-K^+ ATPase), which maintains the electrochemical gradient (and the correct concentrations of Na^+ and K^+) in living cells. The sodium-potassium pump moves two K^+ into the cell while moving three Na^+ out of the cell. The Na+-K+ ATPase exists in two forms, depending on its orientation to the interior or exterior of the cell and its affinity for either sodium or potassium ions. The process consists of the following six steps:

- With the enzyme oriented towards the interior of the cell, the carrier has a high affinity for sodium ions. Three sodium ions bind to the protein.
- ATP is hydrolyzed by the protein carrier, and a low-energy phosphate group attaches to it.
- As a result, the carrier changes shape and re-orients itself towards the exterior of the membrane. The protein's affinity for sodium decreases, and the three sodium ions leave the carrier.
- The shape change increases the carrier's affinity for potassium ions, and two such ions attach to the protein. Subsequently, the low-energy phosphate group detaches from the carrier.
- With the phosphate group removed and potassium ions attached, the carrier protein repositions itself towards the interior of the cell.
- The carrier protein, in its new configuration, has a decreased affinity for potassium, and the two ions are released into the cytoplasm. The protein now has a higher affinity for sodium ions, and the process starts again.

Several things have happened as a result of this process. At this point, there are more sodium ions outside of the cell than inside and more potassium ions inside than out. For every three ions of sodium that move out, two ions of potassium move in. This results in the interior being slightly more negative relative to the exterior. This difference in charge is important in creating the conditions necessary for the secondary process. The sodium-potassium pump is, therefore, an electrogenic pump (a pump that creates a charge imbalance), creating an electrical imbalance across the membrane and contributing to the membrane potential.

Key Points

- The sodium-potassium pump moves K+ into the cell while moving Na+ at a ratio of three Na+ for every two K+ ions.
- When the sodium-potassium- ATPase enzyme points into the cell, it has a high affinity for sodium ions and binds three of them, hydrolyzing ATP and changing shape.
- As the enzyme changes shape, it reorients itself towards the outside of the cell, and the three sodium ions are released.
- The enzyme's new shape allows two potassium to bind and the phosphate group to detach, and the carrier protein repositions itself towards the interior of the cell.
- The enzyme changes shape again, releasing the potassium ions into the cell.
- After potassium is released into the cell, the enzyme binds three sodium ions, which starts the process over again.

Key Terms

- **electrogenic pump**: An ion pump that generates a net charge flow as a result of its activity.
- **Na+-K+ ATPase**: An enzyme located in the plasma membrane of all animal cells that pumps sodium out of cells while pumping potassium into cells.

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4.3C: ABC Transporters

Learning Objectives

- Summarize the function of the three major ABC transporter categories: in prokaryotes, in gram-negative bacteria and the subgroup of ABC proteins

ATP-binding cassette transporters (ABC-transporters) are members of a protein superfamily that is one of the largest and most ancient families with representatives in all extant phyla from prokaryotes to humans. ABC transporters are transmembrane proteins that utilize the energy of adenosine triphosphate (ATP) hydrolysis to carry out certain biological processes including translocation of various substrates across membranes and non-transport-related processes such as translation of RNA and DNA repair. They transport a wide variety of substrates across extra- and intracellular membranes, including metabolic products, lipids and sterols, and drugs. Proteins are classified as ABC transporters based on the sequence and organization of their ATP-binding cassette (ABC) domain(s).

ABC transporters are involved in tumor resistance, cystic fibrosis and a range of other inherited human diseases along with both bacterial (prokaryotic) and eukaryotic (including human) development of resistance to multiple drugs. Bacterial ABC transporters are essential in cell viability, virulence, and pathogenicity.

ABC transporters are divided into three main functional categories. In prokaryotes, importers mediate the uptake of nutrients into the cell. The substrates that can be transported include ions, amino acids, peptides, sugars, and other molecules that are mostly hydrophilic. The membrane-spanning region of the ABC transporter protects hydrophilic substrates from the lipids of the membrane bilayer thus providing a pathway across the cell membrane. In gram-negative bacteria, exporters transport lipids and some polysaccharides from the cytoplasm to the periplasm. Eukaryotes do not possess any importers. Exporters or effluxers, which are both present in prokaryotes and eukaryotes, function as pumps that extrude toxins and drugs out of the cell. The third subgroup of ABC proteins do not function as transporters, but rather are involved in translation and DNA repair processes.

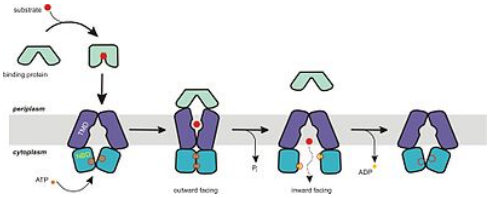

Figure: ***Mechanism of ABC transport****: Proposed mechanism of transport for ABC importers. This alternating-access model was based on the crystal structures of ModBC-A*

In bacterial efflux systems, certain substances that need to be extruded from the cell include surface components of the bacterial cell (e.g. capsular polysaccharides, lipopolysaccharides, and teichoic acid), proteins involved in bacterial pathogenesis (e.g. hemolysis, heme-binding protein, and alkaline protease), heme, hydrolytic enzymes, S-layer proteins, competence factors, toxins, antibiotics, bacteriocins, peptide antibiotics, drugs and siderophores. They also play important roles in biosynthetic pathways, including extracellular polysaccharide biosynthesis and cytochrome biogenesis.

Key Points

- ABC transporters use the energy of ATP hydrolysis to transport substrates across cell membranes.
- Bacterial ABC transporters are essential in cell viability, virulence, and pathogenicity.
- The substrates that can be transported include ions, amino acids, peptides, sugars, and other molecules that are mostly hydrophilic.

Key Terms

- **membrane**: A flexible enclosing or separating tissue forming a plane or film and separating two environments (usually in a plant or animal).
- **hydrolysis**: A chemical process of decomposition involving the splitting of a bond and the addition of the hydrogen cation and the hydroxide anion of water.
- **ATP-binding cassette (ABC) domain**: The ATP-binding cassette (ABC) family is a group of proteins which bind and hydrolyse ATP in order to transport substances across cellular membranes.

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4.3D: Siderophores

Learning Objectives

- Describe the function and variety of siderophores

Iron is essential for almost all living organisms as it is involved in a wide variety of important metabolic processes. However, iron is not always readily available; therefore, microorganisms use various iron uptake systems to secure sufficient supplies from their surroundings. There is considerable variation in the range of iron transporters and iron sources utilized by different microbial species. Pathogens, in particular, require efficient iron acquisition mechanisms to enable them to compete successfully for iron in the highly iron-restricted environment of the host's tissues and body fluids.

Siderophores are small, high-affinity iron chelating compounds secreted by microorganisms such as bacteria, fungi, and grasses. Siderophores are amongst the strongest soluble Fe^{3+} binding agents known. Iron is essential for almost all life, because of its vital role in processes like respiration and DNA synthesis. However, despite being one of the most abundant elements in the Earth's crust, the bioavailability of iron in many environments such as the soil or sea is limited by the very low solubility of the Fe^{3+} ion. This ion state is the predominant one of iron in aqueous, non-acidic, oxygenated environments, and accumulates in common mineral phases such as iron oxides and hydroxides (the minerals that are responsible for red and yellow soil colours). Hence, it cannot be readily utilized by organisms. Microbes release siderophores to scavenge iron from these mineral phases by formation of soluble Fe^{3+}complexes that can be taken up by active transport mechanisms. Many siderophores are nonribosomal peptides, although several are biosynthesised independently.

Siderophores are amongst the strongest binders to Fe^{3+} known, with enterobactin being one of the strongest of these. Because of this property, they have attracted interest from medical science in metal chelation therapy, with the siderophore desferrioxamine B gaining widespread use in treatments for iron poisoning and thalassemia.

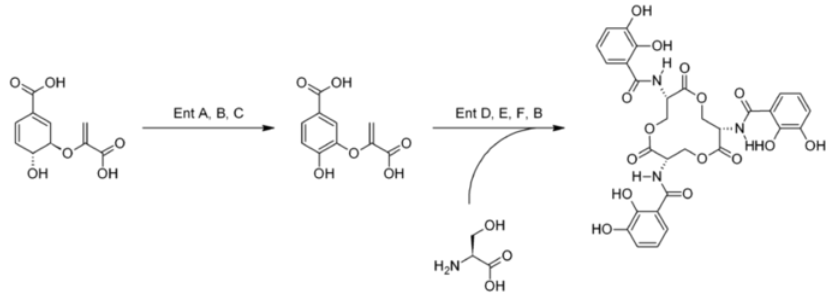

Figure: ***Synthesis of enterobactin****: Enterobactin (also known as Enterochelin) is a high affinity siderophore that acquires iron for microbial systems. It is primarily found in Gram-negative bacteria, such as Escherichia coli and Salmonella typhimurium.*

Iron is tightly bound to proteins such as hemoglobin, transferrin, lactoferrin, and ferritin. There are great evolutionary pressures put on pathogenic bacteria to obtain this metal. For example, the anthrax pathogen *Bacillus anthracis*releases two siderophores, bacillibactin and petrobactin, to scavenge ferric iron from iron proteins. While bacillibactin has been shown to bind to the immune system protein siderocalin, petrobactin is assumed to evade the immune system and has been shown to be important for virulence in mice.

Besides siderophores, some pathogenic bacteria produce *hemophores* (heme binding scavenging proteins) or have receptors that bind directly to iron/heme proteins. In eukaryotes, other strategies to enhance iron solubility and uptake are the acidification of the surrounding (e.g. used by plant roots) or the extracellular reduction of Fe^{3+} into the more soluble Fe^{2+} ions.

Siderophores usually form a stable, hexadentate, octahedral complex with Fe^{3+}preferentially compared to other naturally occurring abundant metal ions, although if there are less than six donor atoms water can also coordinate. The most effective siderophores are those that have three bidentate ligands per molecule, forming a hexadentate complex and causing a smaller entropic change than that caused by chelating a single ferric ion with separate ligands.

Siderophores are usually classified by the ligands used to chelate the ferric iron. The majors groups of siderophores include the catecholates (phenolates), hydroxamates and carboxylates (e.g. derivatives of citric acid). Citric acid can also act as a siderophore. The wide variety of siderophores may be due to evolutionary pressures placed on microbes to produce structurally different siderophores, which cannot be transported by other microbes' specific active transport systems, or in the case of pathogens deactivated by the host organism.

Key Points

- Siderophores are important for some pathogenic bacteria for their acquisition of iron. Many siderophores are nonribosomal peptides, although several are biosynthesised independently.
- The wide variety of siderophores may be due to evolutionary pressures placed on microbes to produce structurally different siderophores which cannot be transported by other microbes' specific active transport systems, or in the case of pathogens deactivated by the host organism.
- Microbes release siderophores to scavenge iron from these mineral phases by formation of soluble Fe^{3+} complexes that can be taken up by active transport mechanisms.

Key Terms

- **siderophores**: Sidereophores are small, high-affinity iron chelating compounds secreted by microorganisms such as bacteria and fungi, and also grasses. Siderophores are amongst the strongest soluble Fe^{3+} binding agents known.

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4.3E: Group Translocation

Group translocation is a protein export or secretion pathway found in plants, bacteria, and archaea.

Learning Objectives

- Recall the following types of transport systems: PEP group translocation and the TAT pathway

Key Points

- PEP is known as a multi-component system that always involves enzymes of the plasma membrane and those in the cytoplasm. An example of this transport is found in E. coli cells.
- The Tat pathway is a protein export, or secretion pathway, that serves to actively translocate folded proteins across a lipid membrane bilayer.
- Systems for secreting proteins across the bacterial outer membrane may be quite complex and play key roles in pathogenesis.

Key Terms

- **phosphotransferase system**: A distinct method used by bacteria for sugar uptake where the source of energy is from phosphoenolpyruvate (PEP).
- **Tat pathway**: A protein export or secretion pathway found in plants, bacteria, and archaea.

With some exceptions, bacteria lack membrane-bound organelles as found in eukaryotes, but they may assemble proteins onto various types of inclusions such as gas vesicles and storage granules. Bacteria may have a single plasma membrane (Gram-positive bacteria) or an inner membrane plus an outer membrane separated by the periplasm (Gram-negative bacteria). Proteins may be incorporated into the plasma membrane. They can also be trapped in either the periplasm or secreted into the environment, according to whether or not there is an outer membrane. The basic mechanism at the plasma membrane is similar to the eukaryotic one. In addition, bacteria may target proteins into or across the outer membrane. Systems for secreting proteins across the bacterial outer membrane may be quite complex. The systems play key roles in pathogenesis. These systems may be described as type I secretion, type II secretion, etc. In most Gram-positive bacteria, certain proteins are targeted for export across the plasma membrane and subsequent covalent attachment to the bacterial cell wall.

A specialized enzyme, sortase, cleaves the target protein at a characteristic recognition site near the protein C-terminus, such as an LPXTG motif (where X can be any amino acid), then transfers the protein onto the cell wall. Several analogous systems are found that also feature a signature motif on the extracytoplasmic face, a C-terminal transmembrane domain, and cluster of basic residues on the cytosolic face at the protein's extreme C-terminus. The PEP-CTERM/exosortase system, found in many Gram-negative bacteria, seems to be related to extracellular polymeric substance production. The PGF-CTERM/archaeosortase A system in archaea is related to S-layer production. The GlyGly-CTERM/rhombosortase system, found in the Shewanella, Vibrio, and a few other genera, seems involved in the release of proteases, nucleases, and other enzymes.

PEP group translocation, also known as the phosphotransferase system or PTS, is a distinct method used by bacteria for sugar uptake where the source of energy is from phosphoenolpyruvate (PEP). It is known as a multi-component system that always involves enzymes of the plasma membrane and those in the cytoplasm. An example of this transport is found in E. coli cells. The system was discovered by Saul Roseman in 1964.

The twin-arginine translocation pathway (Tat pathway) is a protein export or secretion pathway found in plants, bacteria, and archaea. In contrast to the Sec pathway which transports proteins in an unfolded manner, the Tat pathway serves to actively translocate folded proteins across a lipid membrane bilayer. In bacteria, the Tat translocase is found in the cytoplasmic membrane and serves to export proteins to the cell envelope or to the extracellular space. In Gram-negative bacteria the Tat translocase is composed of three essential membrane proteins: TatA, TatB, and TatC. In the most widely studied Tat pathway, that of the Gram-negative bacterium Escherichia coli, these three proteins are expressed from an operon with a fourth Tat protein, TatD, which is not required for Tat function. A fifth Tat protein TatE that is homologous to the TatA protein is present at a much lower level in the cell than TatA. It is not believed to play any significant role in Tat function.

The Tat pathways of Gram-positive bacteria differ in that they do not have a TatB component. In these bacteria the Tat system is made up from a single TatA and TatC component, with the TatA protein being bifunctional and fulfilling the roles of both E. coli TatA and TatB. Not all bacteria carry the tatABC genes in their genome. However, of those that do, there seems to be no discrimination between pathogens and nonpathogens. Despite that fact, some pathogenic bacteria such as Pseudomonas aeruginosa,

Legionella pneumophila, Yersinia pseudotuberculosis, and E. coli O157:H7 rely on a functioning Tat pathway for full virulence in infection models. In addition, a number of exported virulence factors have been shown to rely on the Tat pathway. One such category of virulence factors are the phospholipase C enzymes, which have been shown to be Tat-exported in Pseudomonas aeruginosa and thought to be Tat-exported in Mycobacterium tuberculosis.

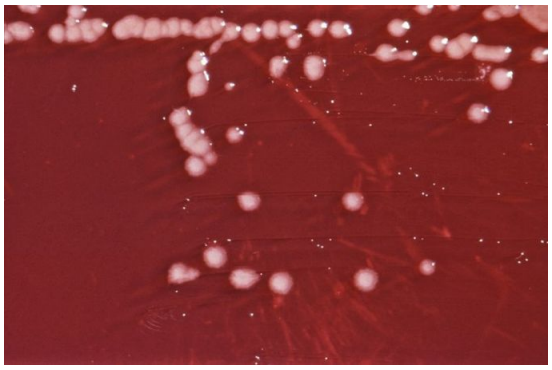

Figure: **Pseudomonas aeruginosa**: P. aeruginosa is capable of growth in diesel and jet fuel, where it is known as a hydrocarbon-using microorganism (or "HUM bug"), causing microbial corrosion. It creates dark, gellish mats sometimes improperly called "algae" because of their appearance.

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SECTION OVERVIEW

4.4: Cell Walls of Prokaryotes

Topic hierarchy

4.4A: The Cell Wall of Bacteria

4.4B: Gram-Negative Outer Membrane

4.4C: Gram-Positive Cell Envelope

4.4D: Mycoplasmas and Other Cell-Wall-Deficient Bacteria

4.4E: Cell Walls of Archaea

4.4F: Damage of the Cell Wall

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4.4A: The Cell Wall of Bacteria

Learning Objectives

- Recall the characteristics of a bacterial cell wall

Bacterial cells lack a membrane bound nucleus. Their genetic material is naked within the cytoplasm. Ribosomes are their only type of organelle. The term “nucleoid” refers to the region of the cytoplasm where chromosomal DNA is located, usually a singular, circular chromosome. Bacteria are usually single-celled, except when they exist in colonies. These ancestral cells reproduce by means of binary fission, duplicating their genetic material and then essentially splitting to form two daughter cells identical to the parent. A wall located outside the cell membrane provides the cell support, and protection against mechanical stress or damage from osmotic rupture and lysis.

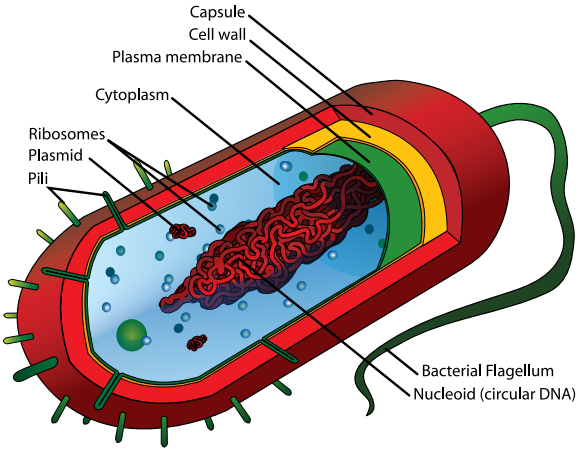

Figure 4.4A.1: Bacterial Cell Wall: The anatomy of bacterial cell structure. (CC BY-SA; via Wikimedia)

The major component of the bacterial cell wall is peptidoglycan or murein. This rigid structure of peptidoglycan, specific only to prokaryotes, gives the cell shape and surrounds the cytoplasmic membrane. Peptidoglycan is a huge polymer of disaccharides (glycan) cross-linked by short chains of identical amino acids (peptides) monomers. The backbone of the peptidoglycan molecule is composed of two derivatives of glucose: N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) with a pentapeptide coming off NAM and varying slightly among bacteria. The NAG and NAM strands are synthesized in the cytosol of the bacteria. They are connected by inter-peptide bridges. They are transported across the cytoplasmic membrane by a carrier molecule called bactoprenol. From the peptidoglycan inwards all bacterial cells are very similar. Going further out, the bacterial world divides into two major classes: Gram positive (Gram +) and Gram negative (Gram -). The cell wall provides important ligands for adherence and receptor sites for viruses or antibiotics.

Key Points

- A cell wall is a layer located outside the cell membrane found in plants, fungi, bacteria, algae, and archaea.
- A peptidoglycan cell wall composed of disaccharides and amino acids gives bacteria structural support.
- The bacterial cell wall is often a target for antibiotic treatment.

Key Terms

- **binary fission**: The process whereby a cell divides asexually to produce two daughter cells.

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4.4B: Gram-Negative Outer Membrane

Learning Objectives

- Recognize the characteristics of a gram-negative bacteria

The Gram-negative cell wall is composed of an outer membrane, a *peptidoglygan* layer, and a *periplasm*.

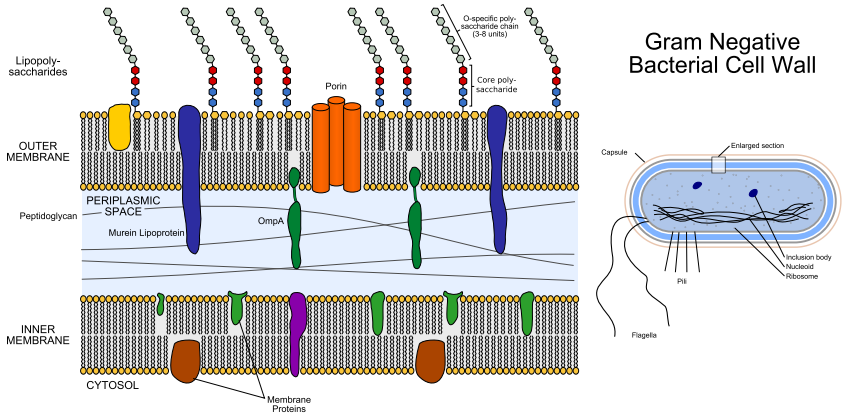

Figure: **Structure of Gram-negative cell wall**: Gram-negative outer membrane composed of lipopolysaccharides.

In the Gram-negative Bacteria the cell wall is composed of a single layer of peptidoglycan surrounded by a membranous structure called the outer membrane. The gram-negative bacteria do not retain crystal violet but are able to retain a counterstain, commonly safranin, which is added after the crystal violet. The safranin is responsible for the red or pink color seen with a gram-negative bacteria. The Gram-negative's cell wall is thinner (10 nanometers thick) and less compact than that of Gram-positive bacteria, but remains strong, tough, and elastic to give them shape and protect them against extreme environmental conditions. The outer membrane of Gram-negative bacteria invariably contains a unique component, lipopolysaccharide (LPS) in addition to proteins and phospholipids. The LPS molecule is toxic and is classified as an endotoxin that elicits a strong immune response when the bacteria infect animals.

In Gram-negative bacteria the outer membrane is usually thought of as part of the outer leaflet of the membrane structure and is relatively permeable. It contains structures that help bacteria adhere to animal cells and cause disease. The peptidoglycan layer is non-covalently anchored to lipoprotein molecules called Braun's lipoproteins through their hydrophobic head. Sandwiched between the outer membrane and the plasma membrane, a concentrated gel-like matrix (the periplasm) is found in the periplasmic space. It is in fact an integral compartment of the gram-negative cell wall and contains binding proteins for amino acids, sugars, vitamins, iron, and enzymes essential for bacterial nutrition. The periplasm space can act as reservoir for virulence factors and a dynamic flux of macromolecules representing the cell's metabolic status and its response to environmental factors. Together, the plasma membrane and the cell wall (outer membrane, peptidoglycan layer, and periplasm) constitute the gram-negative envelope.

Key Points

- The outer membrane of Gram-negative bacteria contains lipopolysaccharides, proteins, and phospholipids.
- The lipopolysaccharide component acts as a virulence factor and causes disease in animals.
- More virulence factors are harbored in the periplasmic space between the outer membrane and the plasma membrane.

Key Terms

- **lipopolysaccharide**: any of a large class of lipids conjugated with polysaccharides
- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.

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4.4C: Gram-Positive Cell Envelope

Gram-positive bacteria have cell envelopes made of a thick layer of peptidoglycans.

Learning Objectives

- Compare and contrast a gram-positive and negative stain

Key Points

- Gram-positive bacteria stain violet by Gram staining due the presence of peptidoglycan in their cell wall.
- Peptidoglycans are attached to negatively-charged lipoteichoic acid monomers important for cell direction and adherence.
- Lipoteichoic acids are covalently linked to lipids within the cytoplasmic membrane, thus connecting the peptidoglycans to the cell cytoplasm.

Key Terms

- **Gram stain**: A method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative).

Gram-positive bacteria are stained dark blue or violet by Gram staining. While Gram staining is a valuable diagnostic tool in both clinical and research settings, not all bacteria can be definitively classified by this technique, thus forming Gram-variable and Gram-indeterminate groups as well.

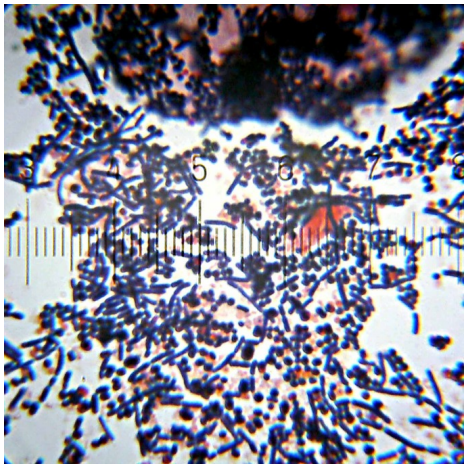

Figure: **Gram-positive bacteria**: These bacteria stain violet by Gram staining.

It is based on the chemical and physical properties of their cell walls. Primarily, it detects peptidoglycan, which is present in a thick layer in Gram-positive bacteria. A Gram-positive results in a purple/blue color while a Gram-negative results in a pink/red color. The Gram stain is almost always the first step in the identification of a bacterial organism, and is the default stain performed by laboratories over a sample when no specific culture is referred.

In Gram-positive bacteria, the cell wall is thick (15-80 nanometers), and consists of several layers of peptidoglycan. They lack the outer membrane envelope found in Gram-negative bacteria. Running perpendicular to the peptidoglycan sheets is a group of molecules called teichoic acids, which are unique to the Gram-positive cell wall. Teichoic acids are linear polymers of polyglycerol or polyribitol substituted with phosphates and a few amino acids and sugars.

The teichoic acid polymers are occasionally anchored to the plasma membrane (called lipoteichoic acid, LTA), and apparently directed outward at right angles to the layers of peptidoglycan. Teichoic acids give the Gram-positive cell wall an overall negative charge due to the presence of phosphodiester bonds between teichoic acid monomers. The functions of teichoic acid are not fully known but it is believed to serve as a chelating agent and means of adherence for the bacteria. These are essential to the viability of Gram-positive bacteria in the environment and provide chemical and physical protection.

One idea is that they provide a channel of regularly-oriented, negative charges for threading positively-charged substances through the complicated peptidoglycan network. Another theory is that teichoic acids are in some way involved in the regulation and assembly of muramic acid sub-units on the outside of the plasma membrane.

There are instances, particularly in the streptococci, wherein teichoic acids have been implicated in the adherence of the bacteria to tissue surfaces and are thought to contribute to the pathogenicity of Gram-positive bacteria.

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4.4D: Mycoplasmas and Other Cell-Wall-Deficient Bacteria

Some bacteria lack a cell wall but retain their ability to survive by living inside another host cell.

Learning Objectives

- Distinguish between bacteria with and without cell walls

Key Points

- Examples of bacteria that lack a cell wall are Mycoplasma and L-form bacteria.
- Mycoplasma is an important cause of disease in animals and is not affected by antibiotic treatments that target cell wall synthesis.
- Mycoplasma acquire cholesterol from the environment and form sterols to build their cytoplasmic membrane.

Key Terms

- **osmotic environment**: environment with controlled net movement of molecules from a region of high solvent concentration to a region of low solvent concentration through a permeable membrane.

For most bacterial cells, the cell wall is critical to cell survival, yet there are some bacteria that do not have cell walls. *Mycoplasma* species are widespread examples and some can be intracellular pathogens that grow inside their hosts. This bacterial lifestyle is called parasitic or saprophytic. Cell walls are unnecessary here because the cells only live in the controlled osmotic environment of other cells. It is likely they had the ability to form a cell wall at some point in the past, but as their lifestyle became one of existence inside other cells, they lost the ability to form walls.

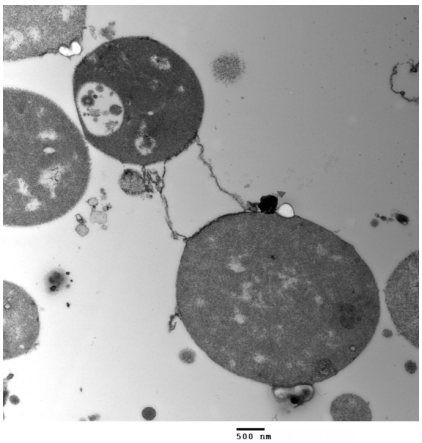

Figure: **L-form bacteria**: L-form bacterial lack a cell wall structure.

Consistent with this very limited lifestyle within other cells, these microbes also have very small genomes. They have no need for the genes for all sorts of biosynthetic enzymes, as they can steal the final components of these pathways from the host. Similarly, they have no need for genes encoding many different pathways for various carbon, nitrogen and energy sources, since their intracellular environment is completely predictable. Because of the absence of cell walls, *Mycoplasma* have a spherical shape and are quickly killed if placed in an environment with very high or very low salt concentrations. However, *Mycoplasma* do have unusually tough membranes that are more resistant to rupture than other bacteria since this cellular membrane has to contend with the host cell factors. The presence of sterols in the membrane contributes to their durability by helping to increase the forces that hold the membrane together. Other bacterial species occasionally mutate or respond to extreme nutritional conditions by forming cells lacking walls, termed L-forms. This phenomenon is observed in both gram-positive and gram-negative species. L-forms have varied shapes and are sensitive to osmotic shock.

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4.4E: Cell Walls of Archaea

Archaeal cell walls differ from bacterial cell walls in their chemical composition and lack of peptidoglycans.

Learning Objectives

- State the similarities between the cell walls of archaea and bacteria

Key Points

- Archaea are single-celled microorganisms that lack a cell nucleus and membrane -bound organelles.
- Like other living organisms, archaea have a semi-rigid cell wall that protects them from the environment.
- The cell wall of archaea is composed of S-layers and lack peptidoglycan molecules with the exception of methanobacteria who have pseudopeptidoglycan in their cell wall.

Key Terms

- **cellulose**: A complex carbohydrate that forms the main constituent of the cell wall in most plants and is important in the manufacture of numerous products, such as paper, textiles, pharmaceuticals, and explosives.
- **chitin**: A complex polysaccharide, a polymer of N-acetylglucosamine, found in the exoskeletons of arthropods and in the cell walls of fungi; thought to be responsible for some forms of asthma in humans.
- **cytoplasm**: The contents of a cell except for the nucleus. It includes cytosol, organelles, vesicles, and the cytoskeleton.

As with other living organisms, archaeal cells have an outer cell membrane that serves as a protective barrier between the cell and its environment. Within the membrane is the cytoplasm, where the living functions of the archeon take place and where the DNA is located. Around the outside of nearly all archaeal cells is a cell wall, a semi-rigid layer that helps the cell maintain its shape and chemical equilibrium. All three of these regions may be distinguished in the cells of bacteria and most other living organisms.

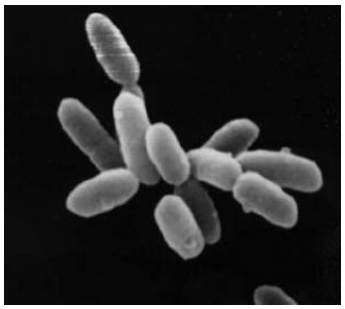

Figure: **Archaea**: Cluster of halobacterium (archaea)

A closer look at each region reveals structural similarities but major differences in chemical composition between bacterial and archaeal cell wall. Archaea builds the same structures as other organisms, but they build them from different chemical components. For instance, the cell walls of all bacteria contain the chemical peptidoglycan. Archaeal cell walls do not contain this compound, though some species contain a similar one. It is assembled from surface-layer proteins called S-layers. Likewise, archaea do not produce walls of cellulose (as do plants) or chitin (as do fungi). The cell wall of archaeans is chemically distinct. Methanogens are the only exception and possess pseudopeptidoglycan chains in their cell wall that lacks amino acids and N-acetylmuramic acid in their chemical composition. The most striking chemical differences between Archaea and other living things lie in their cell membrane. There are four fundamental differences between the archaeal membrane and those of all other cells: (1) chirality of glycerol, (2) ether linkage, (3) isoprenoid chains, and (4) branching of side chains.

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4.4F: Damage of the Cell Wall

The cell wall is responsible for bacterial cell survival and protection against environmental factors and antimicrobial stress.

Learning Objectives

- Discuss the effects that damage to the cell wall has on the bacterial cell

Key Points

- Gram-positive and Gram-negative bacteria are protected by an external cell wall composed of varying layers of peptidoglycan.
- Damage to bacterial cell wall compromises its integrity and creates imbalance of electrolytes that trigger cell death.
- Some antibiotic classes act by inhibiting the synthesis of cell wall building blocks leading to cell lysis and death.

Key Terms

- **hydrolase**: An enzyme that catalyzes the hydrolysis of a substrate.
- **transpeptidase**: Any enzyme that catalyzes the transfer of an amino or peptide group from one molecule to another

The cell wall is the principal stress-bearing and shape-maintaining element in bacteria. Its integrity is thus of critical importance to the viability of a particular cell. In both gram-positive and gram-negative bacteria, the scaffold of the cell wall consists of a cross-linked polymer peptidoglycan. The cell wall of gram-negative bacteria is thin (approximately only 10 nanometers in thickness), and is typically comprised of only two to five layers of peptidoglycan, depending on the growth stage. In gram-positive bacteria, the cell wall is much thicker (20 to 40 nanometers thick).

While the peptidoglycan provides the structural framework of the cell wall, teichoic acids, which make up roughly 50% of the cell wall material, are thought to control the overall surface charge of the wall. This affects murein hydrolase activity, resistance to antibacterial peptides, and adherence to surfaces. Although both of these molecules are polymerized on the surface of the cytoplasmic membrane, their precursors are assembled in the cytoplasm. Any event that interferes with the assembling of the peptidoglycan precursor, and the transport of that object across the cell membrane, where it will integrate into the cell wall, would compromise the integrity of the wall. Damage to the cell wall disturbs the state of cell electrolytes, which can activate death pathways (apoptosis or programmed cell death). Regulated cell death and lysis in bacteria plays an important role in certain developmental processes, such as competence and biofilm development. They also play an important role in the elimination of damaged cells, such as those irreversibly injured by environmental or antibiotic stress. An example of an antibiotic that interferes with bacterial cell wall synthesis is Penicillin. Penicillin acts by binding to transpeptidases and inhibiting the cross-linking of peptidoglycan subunits. A bacterial cell with a damaged cell wall cannot undergo binary fission and is thus certain to die.

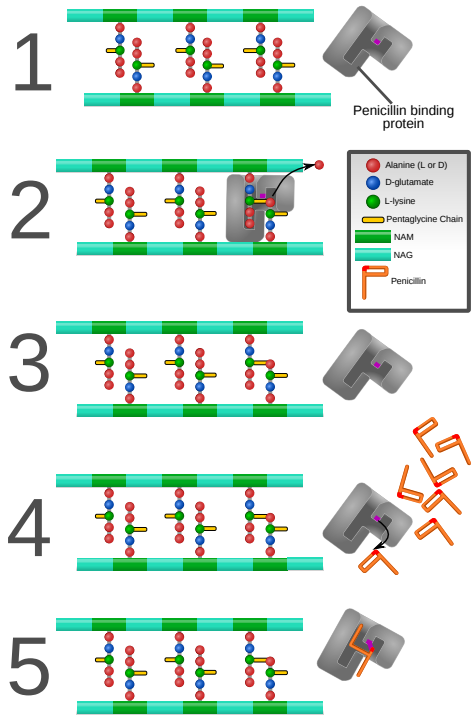

Figure: **Penicillin mechanism of action**: Penicillin acts by binding to penicillin binding proteins and inhibiting the cross-linking of peptidoglycan subunits.

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SECTION OVERVIEW

4.5: Specialized External Structures of Prokaryotes

Topic hierarchy

4.5A: Endospores

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4.5A: Endospores

Learning Objectives

- Describe the function and advantage of endospore formation, as well as the methods for viewing it.

An endospore is a dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum. Endospore formation is usually triggered by lack of nutrients, and usually occurs in Gram-positive bacteria. In endospore formation, the bacterium divides within its cell wall. One side then engulfs the other. Endospores enable bacteria to lie dormant for extended periods, even centuries. When the environment becomes more favorable, the endospore can reactivate itself to the vegetative state. Examples of bacteria that can form endospores include Bacillus and Clostridium. The endospore consists of the bacterium's DNA and part of its cytoplasm, surrounded by a very tough outer coating. Endospores can survive without nutrients. They are resistant to ultraviolet radiation, desiccation, high temperature, extreme freezing and chemical disinfectants. They are commonly found in soil and water, where they may survive for long periods of time. Bacteria produce a single endospore internally.

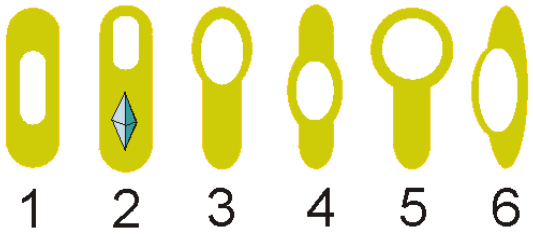

Figure: ***Endospore morphology****: Variations in endospore morphology: (1, 4) central endospore; (2, 3, 5) terminal endospore; (6) lateral endospore.*

Viewing endospores under the light microscope can be difficult due to the impermeability of the endospore wall to dyes and stains. While the rest of a bacterial cell may stain, the endospore is left colorless. To combat this, a special stain technique called a Moeller stain is used. That allows the endospore to show up as red, while the rest of the cell stains blue. Another staining technique for endospores is the Schaeffer-Fulton stain, which stains endospores green and bacterial bodies red. There are variations in endospore morphology. Examples of bacteria having terminal endospores include Clostridium tetani, the pathogen that causes the disease tetanus. Bacteria having a centrally placed endospore include Bacillus cereus, and those having a subterminal endospore include Bacillus subtilis. Sometimes the endospore can be so large that the cell can be distended around the endospore. This is typical of Clostridium tetani.

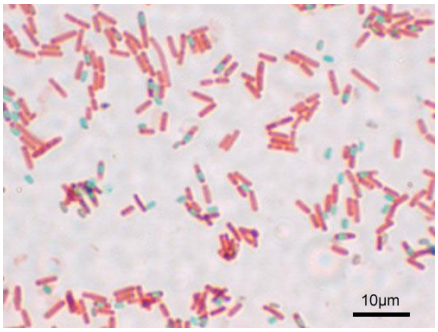

Figure: **Bacillus subtilis stained with the Schaeffer-Fulton stain.**: A stained preparation of Bacillus subtilis showing endospores as green and the vegetative cell as red.

When a bacterium detects environmental conditions are becoming unfavorable it may start the process of endosporulation, which takes about eight hours. The DNA is replicated and a membrane wall known as a spore septum begins to form between it and the rest of the cell. The plasma membrane of the cell surrounds this wall and pinches off to leave a double membrane around the DNA, and the developing structure is now known as a *forespore*. Calcium dipicolinate is incorporated into the forespore during this time. Next the peptidoglycan cortex forms between the two layers and the bacterium adds a spore coat to the outside of the forespore. Sporulation is now complete, and the mature endospore will be released when the surrounding vegetative cell is degraded.

While resistant to extreme heat and radiation, endospores can be destroyed by burning or by autoclaving. Endospores are able to survive boiling at 100°C for hours, although the longer the number of hours the fewer that will survive. An indirect way to destroy

them is to place them in an environment that reactivates them to their vegetative state. They will germinate within a day or two with the right environmental conditions, and then the vegetative cells can be straightforwardly destroyed. This indirect method is called Tyndallization. It was the usual method for a while in the late 19th century before the advent of inexpensive autoclaves. Prolonged exposure to ionising radiation, such as x-rays and gamma rays, will also kill most endospores.

Reactivation of the endospore occurs when conditions are more favourable and involves activation, germination, and outgrowth. Even if an endospore is located in plentiful nutrients, it may fail to germinate unless activation has taken place. This may be triggered by heating the endospore. Germination involves the dormant endospore starting metabolic activity and thus breaking hibernation. It is commonly characterised by rupture or absorption of the spore coat, swelling of the endospore, an increase in metabolic activity, and loss of resistance to environmental stress.

As a simplified model for cellular differentiation, the molecular details of endospore formation have been extensively studied, specifically in the model organism Bacillus subtilis. These studies have contributed much to our understanding of the regulation of gene expression, transcription factors, and the sigma factor subunits of RNA polymerase.

Endospores of the bacterium Bacillus anthracis were used in the 2001 anthrax attacks. The powder found in contaminated postal letters was composed of extracellular anthrax endospores. Inhalation, ingestion or skin contamination of these endospores led to a number of deaths.

Geobacillus stearothermophilus endospores are used as biological indicators when an autoclave is used in sterilization procedures. Bacillus subtilis spores are useful for the expression of recombinant proteins and in particular for the surface display of peptides and proteins as a tool for fundamental and applied research in the fields of microbiology, biotechnology and vaccination.

Key Points

- Examples of bacteria that can form endospores include Bacillus and Clostridium.
- Endospores can survive without nutrients. They are resistant to ultraviolet radiation, desiccation, high temperature, extreme freezing and chemical disinfectants.
- While resistant to extreme heat and radiation, endospores can be destroyed by burning or by autoclaving.

Key Terms

- **endospore**: A dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.

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SECTION OVERVIEW

4.6: Specialized Internal Structures of Prokaryotes

Topic hierarchy

4.6A: Ribosomes

4.6B: Cell Inclusions and Storage Granules

4.6C: Carboxysomes

4.6D: Magnetosomes

4.6E: Gas Vesicles

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4.6A: Ribosomes

Learning Objectives

- Compare and contrast ribosome structure and function in prokaryotes and eukaryotes

Ribosomes are tiny spherical organelles that make proteins by joining amino acids together. Many ribosomes are found free in the cytosol, while others are attached to the rough endoplasmic reticulum. The purpose of the ribosome is to translate messenger RNA (mRNA) to proteins with the aid of tRNA. In eukaryotes, ribosomes can commonly be found in the cytosol of a cell, the endoplasmic reticulum or mRNA, as well as the matrix of the mitochondria. Proteins synthesized in each of these locations serve a different role in the cell. In prokaryotes, ribosomes can be found in the cytosol as well. This protein-synthesizing organelle is the only organelle found in both prokaryotes and eukaryotes, asserting the fact that the ribosome is a trait that evolved early on, most likely present in the common ancestor of eukaryotes and prokaryotes. Ribosomes are not membrane bound.

Ribosomes are composed of two subunits, one large and one small, that only bind together during protein synthesis. The purpose of the ribosome is to take the actual message and the charged aminoacyl-tRNA complex to generate the protein. To do so, they have three binding sites. One is for the mRNA; the other two are for the tRNA. The binding sites for tRNA are the A site, which holds the aminoacyl-tRNA complex, and the P site, which binds to the tRNA attached to the growing polypeptide chain.

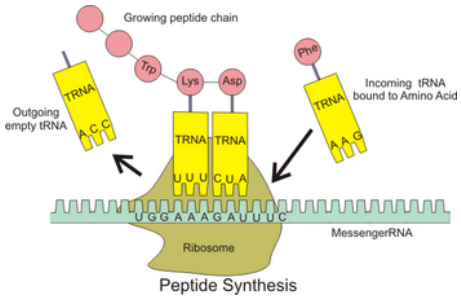

Figure: **Peptide synthesis by a ribosome.**: The ribosome assembles amino acids into a protein. The specific amino acids are controlled by the mRNA sequence. This is required by all living cells and associated viruses.

In most bacteria, the most numerous intracellular structure is the ribosome which is the site of protein synthesis in all living organisms. All prokaryotes have 70S (where S=Svedberg units) ribosomes while eukaryotes contain larger 80S ribosomes in their cytosol. The 70S ribosome is made up of a 50S and 30S subunits. The 50S subunit contains the 23S and 5S rRNA while the 30S subunit contains the 16S rRNA. These rRNA molecules differ in size in eukaryotes and are complexed with a large number of ribosomal proteins, the number and type of which can vary slightly between organisms. The ribosome is the most commonly observed intracellular multiprotein complex in bacteria.

Ribosome assembly consists of transcription, translation, the folding of rRNA and ribosomal proteins, the binding of ribosomal proteins, and the binding and release of the assembly components to make the ribosome. In vivo assembly of the 30S subunit has two intermediates (p130S and p230S) and the 50S subunit has three intermediates (p150S, p250S, and p350S). However, the reconstitution intermediates are not the same as in vitro. The intermediates of the 30S subunit yield 21S and 30S particles while the intermediates of the 50S subunit yield 32S, 43S, and 50S particles. The intermediates in the in vivo assembly are precursor rRNA which is different from in vitro which uses matured rRNA. To complete the mechanism of ribosome assembly, these precursor rRNA gets transformed in the polysomes.

Key Points

- All prokaryotes have 70S (where S=Svedberg units) ribosomes while eukaryotes contain larger 80S ribosomes in their cytosol. The 70S ribosome is made up of a 50S and 30S subunits.
- Ribosomes play a key role in the catalysis of two important and crucial biological processes. peptidyl transfer and peptidyl hydrolysis.
- Ribosomes are tiny spherical organelles that make proteins by joining amino acids together. Many ribosomes are found free in the cytosol, while others are attached to the rough endoplasmic reticulum.

Key Terms

- **ribosome**: Small organelles found in all cells; involved in the production of proteins by translating messenger RNA.
- **translation**: A process occurring in the ribosome, in which a strand of messenger RNA (mRNA) guides assembly of a sequence of amino acids to make a protein.
- **Svedberg**: The Svedberg unit (S) offers a measure of particle size based on its rate of travel in a tube subjected to high g-force.

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4.6B: Cell Inclusions and Storage Granules

Bacteria have different methods of nutrient storage that are employed in times of plenty, for use in times of want.

Learning Objectives

- Explain the hypothesis regarding the formation of inclusion bodies and the importance of storage granules

Key Points

- Sulfur granules are especially common in bacteria that use hydrogen sulfide as an electron source.
- When genes from one organism are expressed in another, the resulting protein sometimes forms inclusion bodies.
- Many bacteria store excess carbon in the form of polyhydroxyalkanoates or glycogen.

Key Terms

- **Inclusion bodies**: Inclusion bodies are nuclear or cytoplasmic aggregates of stainable substances, usually proteins.

Cell Inclusions and Storage Granules

Bacteria, despite their simplicity, contain a well-developed cell structure responsible for many unique biological properties not found among archaea or eukaryotes. Because of the simplicity of bacteria relative to larger organisms, and the ease with which they can be manipulated experimentally, the cell structure of bacteria has been well studied, revealing many biochemical principles that have been subsequently applied to other organisms.

Most bacteria do not live in environments that contain large amounts of nutrients at all times. To accommodate these transient levels of nutrients, bacteria contain several different methods of nutrient storage that are employed in times of plenty, for use in times of want. For example, many bacteria store excess carbon in the form of polyhydroxyalkanoates or glycogen. Some microbes store soluble nutrients, such as nitrate in vacuoles. Sulfur is most often stored as elemental (S0) granules which can be deposited either intra- or extracellularly. Sulfur granules are especially common in bacteria that use hydrogen sulfide as an electron source. Most of the above mentioned examples can be viewed using a microscope, and are surrounded by a thin non-unit membrane to separate them from the cytoplasm.

Inclusion bodies are nuclear or cytoplasmic aggregates of stainable substances, usually proteins. They typically represent sites of viral multiplication in a bacterium or a eukaryotic cell, and usually consist of viral capsid proteins. Inclusion bodies have a non-unit lipid membrane. Protein inclusion bodies are classically thought to contain misfolded protein. However, this has recently been contested, as green fluorescent protein will sometimes fluoresce in inclusion bodies, which indicates some resemblance of the native structure and researchers have recovered folded protein from inclusion bodies.

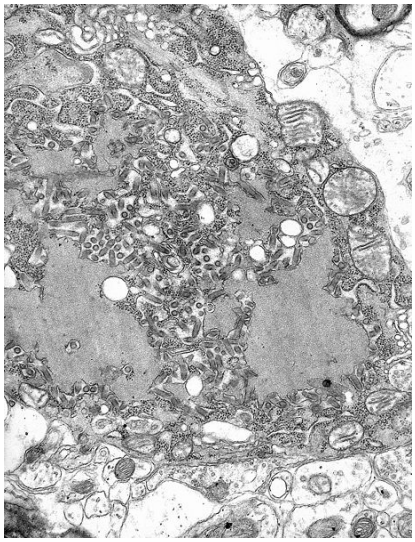

Figure: **Electron Micrograph of the Rabies Virus.**: This electron micrograph shows the rabies virus, as well as Negri bodies, or cellular inclusions.

When genes from one organism are expressed in another the resulting protein sometimes forms inclusion bodies. This is often true when large evolutionary distances are crossed; for example, a cDNA isolated from Eukarya and expressed as a recombinant gene in a prokaryote, risks the formation of the inactive aggregates of protein known as inclusion bodies. While the cDNA may properly code for a translatable mRNA, the protein that results will emerge in a foreign microenvironment. This often has fatal effects, especially if the intent of cloning is to produce a biologically active protein. For example, eukaryotic systems for carbohydrate modification and membrane transport are not found in prokaryotes.

The internal microenvironment of a prokaryotic cell (pH, osmolarity) may differ from that of the original source of the gene. Mechanisms for folding a protein may also be absent, and hydrophobic residues that normally would remain buried may be exposed and available for interaction with similar exposed sites on other ectopic proteins. Processing systems for the cleavage and removal of internal peptides would also be absent in bacteria. The initial attempts to clone insulin in a bacterium suffered all of these deficits. In addition, the fine controls that may keep the concentration of a protein low will also be missing in a prokaryotic cell, and overexpression can result in filling a cell with ectopic protein that, even if it were properly folded, would precipitate by saturating its environment.

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4.6C: Carboxysomes

Learning Objectives

- Generalize the function of carboxysomes in autotrophic bacteria

Carboxysomes are intracellular structures found in many autotrophic bacteria, including Cyanobacteria, Knallgasbacteria, Nitroso- and Nitrobacteria. They are proteinaceous structures resembling phage heads in their morphology; they contain the enzymes of carbon dioxide fixation in these organisms. It is thought that the high local concentration of the enzymes, along with the fast conversion of bicarbonate to carbon dioxide by carbonic anhydrase, allows faster and more efficient carbon dioxide fixation than is possible inside the cytoplasm. Similar structures are known to harbor the B_{12}-containing coenzyme glycerol dehydratase, the key enzyme of glycerol fermentation to 1,3-propanediol, in some Enterobacteriaceae, such as Salmonella.

Carboxysomes are bacterial microcompartments that contain enzymes involved in carbon fixation. Carboxysomes are made of polyhedral protein shells about 80 to 140 nanometres in diameter. These compartments are thought to concentrate carbon dioxide to overcome the inefficiency of RuBisCo (ribulose bisphosphate carboxylase/oxygenase) – the predominant enzyme in carbon fixation and the rate limiting enzyme in the Calvin cycle. These organelles are found in all cyanobacteria and many chemotrophic bacteria that fix carbon dioxide.

Carboxysomes are an example of a wider group of protein micro-compartments that have dissimilar functions but similar structures, based on homology of the two shell protein families. Using electron microscopy the first carboxysomes were seen in 1956, in the cyanobacterium Phormidium uncinatum. In the early 1960s, similar polyhedral objects were observed in other cyanobacteria. These structures were named polyhedral bodies in 1961; over the next few years they were also discovered in some chemotrophic bacteria that fixed carbon dioxide. Among these are *Halothiobacillus*, *Acidithiobacillus*, *Nitrobacter* and *Nitrococcus*.

Carboxysomes were first purified from Thiobacillus neapolitanus in 1973, and were shown to contain RuBisCo held within a rigid outer covering.

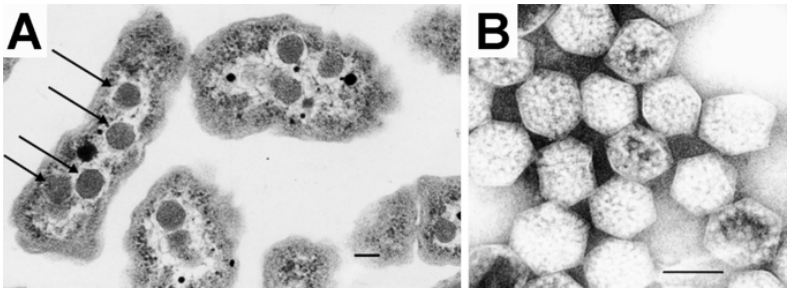

Figure: ***Electron Micrograph of a carboxysome****: (A) A thin-section electron micrograph of H. neapolitanus cells with carboxysomes inside. In one of the cells shown, arrows highlight the visible carboxysomes. (B) A negatively stained image of intact carboxysomes isolated from H. neapolitanus. The features visualized arise from the distribution of stain around proteins forming the shell as well as around the RuBisCO molecules that fill the carboxysome interior. Scale bars indicate 100 nm.*

Key Points

- Carboxysomes are proteinaceous structures resembling phage heads in their morphology and contain the enzymes of carbon dioxide fixation in these organisms.
- Carboxysomes are made of polyhedral protein shells about 80 to 140 nanometres in diameter.
- These organelles are found in all cyanobacteria and many chemotrophic bacteria that fix carbon dioxide.

Key Terms

- **carboxysome**: A bacterial organelle that contains enzymes involved in carbon fixation.

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4.6D: Magnetosomes

Learning Objectives

- Illustrate the structure of magnetosomes and the advantages that they provide to magentotactic bacteria

Magnetosomes are intracellular organelles found in magnetotactic bacteria that allow them to sense and align themselves along a magnetic field (magnetotaxis). They contain 15 to 20 magnetite crystals that together act like a compass needle to orient magnetotactic bacteria in geomagnetic fields, thereby simplifying their search for their preferred microaerophilic environments. Each magnetite crystal within a magnetosome is surrounded by a lipid bilayer. Specific soluble and transmembrane proteins are sorted to the membrane. Recent research has shown that magnetosomes are invaginations of the inner membrane and not freestanding vesicles. Magnetite-bearing magnetosomes have also been found in eukaryotic magnetotactic algae, with each cell containing several thousand crystals.

Magnetotactic bacteria usually mineralize either iron oxide magnetosomes, which contain crystals of magnetite (Fe_3O_4), or iron sulfide magnetosomes, which contain crystals of greigite (Fe_3S_4). Several other iron sulfide minerals have also been identified in iron sulfide magnetosomes — including mackinawite (tetragonal FeS) and a cubic FeS — which are thought to be precursors of Fe3S4. One type of magnetotactic bacterium present at the oxic-anoxic transition zone (OATZ) of the southern basin of the Pettaquamscutt River Estuary, Narragansett, Rhode Island is known to produce both iron oxide and iron sulfide magnetosomes.



Figure: ***Magnetospirilli with black magnetosome chains faintly visible****: There is a broad range of shapes and groups of magnetic bacteria. However, cultivation of these organisms in the laboratory is often difficult. Only a few strains of magnetotactic bacteria have been isolated in pure culture, a tiny minority of the vast diversity of naturally occurring populations from largely unexplored natural habitats such as the marine environment.*

The particle morphology of magnetosome crystals varies, but is consistent within cells of a single magnetotactic bacterial species or strain. Three general crystal morphologies have been reported in magnetotactic bacteria on the basis: roughly cuboidal, elongated prismatic (roughly rectangular), and tooth-, bullet-, or arrowhead-shaped. Magnetosome crystals are typically 35–120 nm long, which makes them single- domain. Single-domain crystals have the maximum possible magnetic moment per unit volume for a given composition. Smaller crystals are superparamagnetic–that is, not permanently magnetic at ambient temperature, and domain walls would form in larger crystals. In most magnetotactic bacteria, the magnetosomes are arranged in one or more chains.

Magnetic interactions between the magnetosome crystals in a chain cause their magnetic dipole moments to orientate parallel to each other along the length of the chain. The magnetic dipole moment of the cell is usually large enough so that its interaction with Earth's magnetic field overcomes thermal forces that tend to randomize the orientation of the cell in its aqueous surroundings. Magnetotactic bacteria also use aerotaxis, a response to changes in oxygen concentration that favors swimming toward a zone of optimal oxygen concentration. In lakes or oceans the oxygen concentration is commonly dependent on depth. As long as the Earth's magnetic field has a significant downward slant, the orientation along field lines aids the search for the optimal concentration. This process is called magneto-aerotaxis.

Key Points

- Magnetosomes contain 15 to 20 magnetite crystals that together act like a compass needle to orient magnetotactic bacteria in geomagnetic fields, thereby simplifying their search for their preferred microaerophilic environments.
- The particle morphology of magnetosome crystals varies, but is consistent within cells of a single magnetotactic bacterial species or strain.
- Each magnetite crystal within a magnetosome is surrounded by a lipid bilayer. Specific soluble and transmembrane proteins are sorted to the membrane.

Key Terms

- **magnetotaxis**: The supposed ability to sense a magnetic field and coordinate movement in response, later discovered to be natural magnetism: such creatures orient themselves magnetically even after death.
- **magnetosome**: A membranous prokaryotic organelle, containing mineral crystals, present in magnetotactic bacteria.

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4.6E: Gas Vesicles

Learning Objectives

- Discuss the role of a gas vesicle in regards to survival.

Gas vesicles are spindle-shaped structures found in some planktonic bacteria that provides buoyancy to these cells by decreasing their overall cell density. Positive buoyancy is needed to keep the cells in the upper reaches of the water column, so that they can continue to perform photosynthesis. They are made up of a shell of protein that has a highly hydrophobic inner surface, making it impermeable to water (and stopping water vapor from condensing inside), but permeable to most gases. Because the gas vesicle is a hollow cylinder, it is liable to collapse when the surrounding pressure becomes too great.

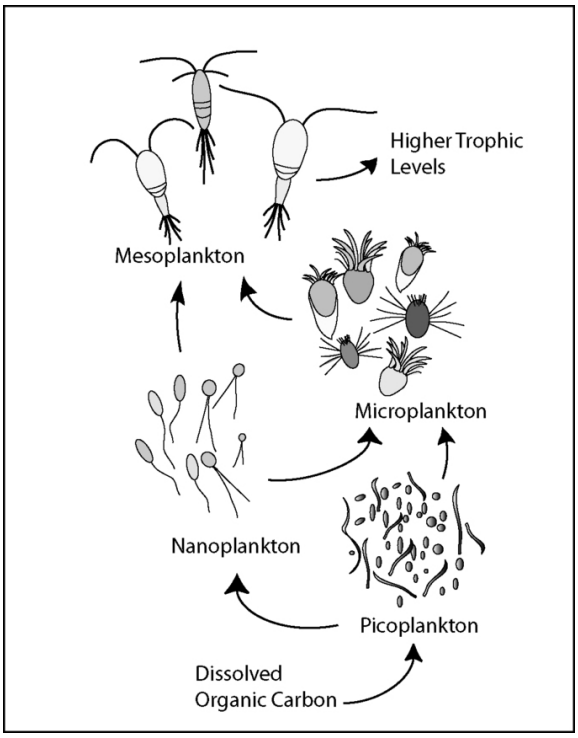

Figure: **Illustration of a microbial loop**: Gas vesicles provide bouyancy for some planktonic bacteria by decreasing their overall cell density.

Natural selection has fine-tuned the structure of the gas vesicle to maximize its resistance to buckling by including an external strengthening protein, GvpC, rather like the green thread in a braided hosepipe. There is a simple relationship between the diameter of the gas vesicle and pressure at which it will collapse – the wider the gas vesicle the weaker it becomes. However, wider gas vesicles are more efficient. They provide more buoyancy per unit of protein than narrow gas vesicles. Different species produce gas vesicles of different diameters, allowing them to colonize different depths of the water column (fast growing, highly competitive species with wide gas vesicles in the top most layers; slow growing, dark-adapted, species with strong narrow gas vesicles in the deeper layers). The diameter of the gas vesicle will also help determine which species survive in different bodies of water. Deep lakes that experience winter mixing will expose the cells to the hydrostatic pressure generated by the full water column. This will select for species with narrower, stronger gas vesicles.

Key Points

- They are made up of a shell of protein that has a highly hydrophobic inner surface, making it impermeable to water (and stopping water vapour from condensing inside), but permeable to most gases.
- Natural selection has fine tuned the structure of the gas vesicle to maximize its resistance to buckling, including an external strengthening protein, GvpC, rather like the green thread in a braided hosepipe.
- The diameter of the gas vesicle will also help determine which species survive in different bodies of water.

Key Terms

- **gas vesicle**: Gas vesicles are spindle-shaped structures found in some planktonic bacteria that provide buoyancy to these cells by decreasing their overall cell density.
- **gas gangrene**: a bacterial infection that produces gas in tissues in necrotizing or rotting tissues

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SECTION OVERVIEW

4.7: Internal Structures of Eukaryotic Cells

Topic hierarchy

4.7A: The Nucleus and Ribosomes

4.7B: Mitochondria

4.7C: Comparing Plant and Animal Cells

4.7D: The Endoplasmic Reticulum

4.7E: The Golgi Apparatus

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4.7A: The Nucleus and Ribosomes

Found within eukaryotic cells, the nucleus contains the genetic material that determines the entire structure and function of that cell.

Learning Objectives

- Explain the purpose of the nucleus in eukaryotic cells

Key Points

- The nucleus contains the cell ‘s DNA and directs the synthesis of ribosomes and proteins.
- Found within the nucleoplasm, the nucleolus is a condensed region of chromatin where ribosome synthesis occurs.
- Chromatin consists of DNA wrapped around histone proteins and is stored within the nucleoplasm.
- Ribosomes are large complexes of protein and ribonucleic acid (RNA) responsible for protein synthesis when DNA from the nucleus is transcribed.

Key Terms

- **histone**: any of various simple water-soluble proteins that are rich in the basic amino acids lysine and arginine and are complexed with DNA in the nucleosomes of eukaryotic chromatin
- **nucleolus**: a conspicuous, rounded, non-membrane bound body within the nucleus of a cell
- **chromatin**: a complex of DNA, RNA, and proteins within the cell nucleus out of which chromosomes condense during cell division

The Nucleus

One of the main differences between prokaryotic and eukaryotic cells is the nucleus. As previously discussed, prokaryotic cells lack an organized nucleus while eukaryotic cells contain membrane-bound nuclei (and organelles) that house the cell’s DNA and direct the synthesis of ribosomes and proteins.

The nucleus stores chromatin (DNA plus proteins) in a gel-like substance called the nucleoplasm. To understand chromatin, it is helpful to first consider chromosomes. Chromatin describes the material that makes up chromosomes, which are structures within the nucleus that are made up of DNA, the hereditary material. You may remember that in prokaryotes, DNA is organized into a single circular chromosome. In eukaryotes, chromosomes are linear structures. Every eukaryotic species has a specific number of chromosomes in the nuclei of its body’s cells. For example, in humans, the chromosome number is 46, while in fruit flies, it is eight. Chromosomes are only visible and distinguishable from one another when the cell is getting ready to divide. In order to organize the large amount of DNA within the nucleus, proteins called histones are attached to chromosomes; the DNA is wrapped around these histones to form a structure resembling beads on a string. These protein-chromosome complexes are called chromatin.

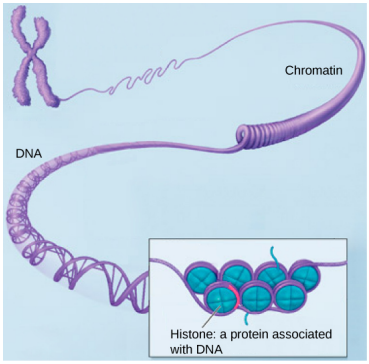

Figure: **DNA is highly organized**: This image shows various levels of the organization of chromatin (DNA and protein). Along the chromatin threads, unwound protein-chromosome complexes, we find DNA wrapped around a set of histone proteins.

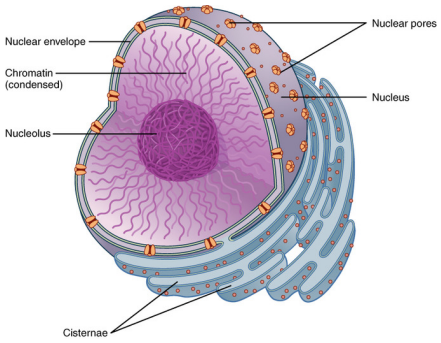

Figure: **The nucleus stores the hereditary material of the cell**: The nucleus is the control center of the cell. The nucleus of living cells contains the genetic material that determines the entire structure and function of that cell.

The nucleoplasm is also where we find the nucleolus. The nucleolus is a condensed region of chromatin where ribosome synthesis occurs. Ribosomes, large complexes of protein and ribonucleic acid (RNA), are the cellular organelles responsible for protein synthesis. They receive their "orders" for protein synthesis from the nucleus where the DNA is transcribed into messenger RNA (mRNA). This mRNA travels to the ribosomes, which translate the code provided by the sequence of the nitrogenous bases in the mRNA into a specific order of amino acids in a protein.

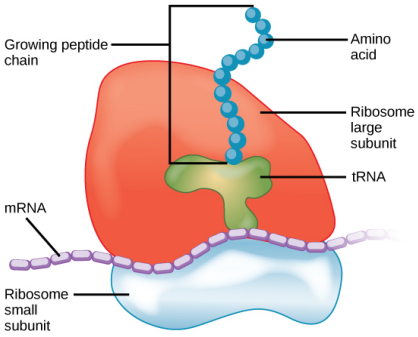

Figure: **Ribosomes are responsible for protein synthesis**: Ribosomes are made up of a large subunit (top) and a small subunit (bottom). During protein synthesis, ribosomes assemble amino acids into proteins.

Lastly, the boundary of the nucleus is called the nuclear envelope. It consists of two phospholipid bilayers: an outer membrane and an inner membrane. The nuclear membrane is continuous with the endoplasmic reticulum, while nuclear pores allow substances to enter and exit the nucleus.

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4.7B: Mitochondria

Learning Objectives

- Explain the role of the mitochondria.

One of the major features distinguishing prokaryotes from eukaryotes is the presence of mitochondria. Mitochondria are double-membraned organelles that contain their own ribosomes and DNA. Each membrane is a phospholipid bilayer embedded with proteins. Eukaryotic cells may contain anywhere from one to several thousand mitochondria, depending on the cell's level of energy consumption. Each mitochondrion measures 1 to 10 micrometers (or greater) in length and exists in the cell as an organelle that can be ovoid to worm-shaped to intricately branched.

Mitochondria Structure

Most mitochondria are surrounded by two membranes, which would result when one membrane-bound organism was engulfed into a vacuole by another membrane-bound organism. The mitochondrial inner membrane is extensive and involves substantial infoldings called cristae that resemble the textured, outer surface of alpha-proteobacteria. The matrix and inner membrane are rich with the enzymes necessary for aerobic respiration.

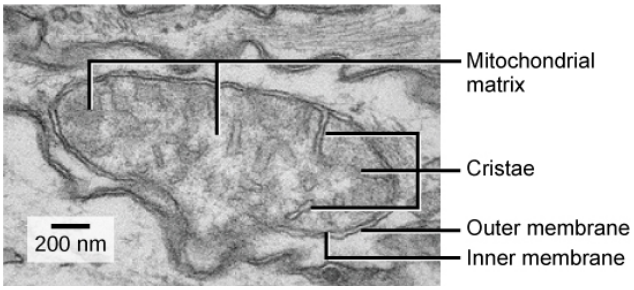

Figure: ***Mitochondrial structure****: This electron micrograph shows a mitochondrion as viewed with a transmission electron microscope. This organelle has an outer membrane and an inner membrane. The inner membrane contains folds, called cristae, which increase its surface area. The space between the two membranes is called the intermembrane space, and the space inside the inner membrane is called the mitochondrial matrix. ATP synthesis takes place on the inner membrane.*

Mitochondria have their own (usually) circular DNA chromosome that is stabilized by attachments to the inner membrane and carries genes similar to genes expressed by alpha-proteobacteria. Mitochondria also have special ribosomes and transfer RNAs that resemble these components in prokaryotes. These features all support the hypothesis that mitochondria were once free-living prokaryotes.

Mitochondria Function

Mitochondria are often called the "powerhouses" or "energy factories" of a cell because they are responsible for making adenosine triphosphate (ATP), the cell's main energy-carrying molecule. ATP represents the short-term stored energy of the cell. Cellular respiration is the process of making ATP using the chemical energy found in glucose and other nutrients. In mitochondria, this process uses oxygen and produces carbon dioxide as a waste product. In fact, the carbon dioxide that you exhale with every breath comes from the cellular reactions that produce carbon dioxide as a by-product.

It is important to point out that muscle cells have a very high concentration of mitochondria that produce ATP. Your muscle cells need a lot of energy to keep your body moving. When your cells don't get enough oxygen, they do not make a lot of ATP. Instead, the small amount of ATP they make in the absence of oxygen is accompanied by the production of lactic acid. In addition to the aerobic generation of ATP, mitochondria have several other metabolic functions. One of these functions is to generate clusters of iron and sulfur that are important cofactors of many enzymes. Such functions are often associated with the reduced mitochondrion-derived organelles of anaerobic eukaryotes.

Origins of Mitochondria

There are two hypotheses about the origin of mitochondria: *endosymbiotic* and *autogenous*, but the most accredited theory at present is endosymbiosis. The endosymbiotic hypothesis suggests mitochondria were originally prokaryotic cells, capable of

implementing oxidative mechanisms. These prokaryotic cells may have been engulfed by a eukaryote and became endosymbionts living inside the eukaryote.

Key Points

- Mitochondria contain their own ribosomes and DNA; combined with their double membrane, these features suggest that they might have once been free-living prokaryotes that were engulfed by a larger cell.
- Mitochondria have an important role in cellular respiration through the production of ATP, using chemical energy found in glucose and other nutrients.
- Mitochondria are also responsible for generating clusters of iron and sulfur, which are important cofactors of many enzymes.

Key Terms

- **alpha-proteobacteria**: A taxonomic class within the phylum Proteobacteria — the phototropic proteobacteria.
- **adenosine triphosphate**: a multifunctional nucleoside triphosphate used in cells as a coenzyme, often called the “molecular unit of energy currency” in intracellular energy transfer
- **cofactor**: an inorganic molecule that is necessary for an enzyme to function

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4.7C: Comparing Plant and Animal Cells

Although they are both eukaryotic cells, there are unique structural differences between animal and plant cells.

Learning Objectives

- Differentiate between the structures found in animal and plant cells

Key Points

- Centrosomes and lysosomes are found in animal cells, but do not exist within plant cells.
- The lysosomes are the animal cell's "garbage disposal", while in plant cells the same function takes place in vacuoles.
- Plant cells have a cell wall, chloroplasts and other specialized plastids, and a large central vacuole, which are not found within animal cells.
- The cell wall is a rigid covering that protects the cell, provides structural support, and gives shape to the cell.
- The chloroplasts, found in plant cells, contain a green pigment called chlorophyll, which captures the light energy that drives the reactions of plant photosynthesis.
- The central vacuole plays a key role in regulating a plant cell's concentration of water in changing environmental conditions.

Key Terms

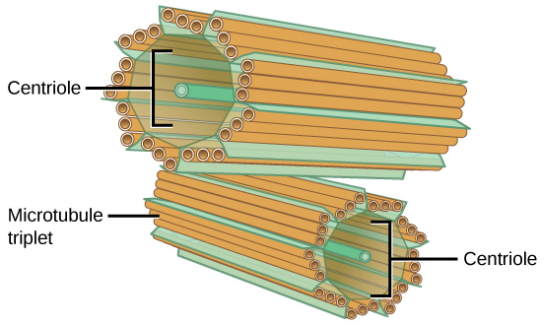
- **protist**: Any of the eukaryotic unicellular organisms including protozoans, slime molds and some algae; historically grouped into the kingdom Protoctista.
- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy
- **heterotroph**: an organism that requires an external supply of energy in the form of food, as it cannot synthesize its own

Animal Cells versus Plant Cells

Each eukaryotic cell has a plasma membrane, cytoplasm, a nucleus, ribosomes, mitochondria, peroxisomes, and in some, vacuoles; however, there are some striking differences between animal and plant cells. While both animal and plant cells have microtubule organizing centers (MTOCs), animal cells also have centrioles associated with the MTOC: a complex called the centrosome. Animal cells each have a centrosome and lysosomes, whereas plant cells do not. Plant cells have a cell wall, chloroplasts and other specialized plastids, and a large central vacuole, whereas animal cells do not.

The Centrosome

The centrosome is a microtubule-organizing center found near the nuclei of animal cells. It contains a pair of centrioles, two structures that lie perpendicular to each other. Each centriole is a cylinder of nine triplets of microtubules. The centrosome (the organelle where all microtubules originate) replicates itself before a cell divides, and the centrioles appear to have some role in pulling the duplicated chromosomes to opposite ends of the dividing cell. However, the exact function of the centrioles in cell division isn't clear, because cells that have had the centrosome removed can still divide; and plant cells, which lack centrosomes, are capable of cell division.



The Centrosome Structure: The centrosome consists of two centrioles that lie at right angles to each other. Each centriole is a cylinder made up of nine triplets of microtubules. Nontubulin proteins (indicated by the green lines) hold the microtubule triplets together.

Lysosomes

Animal cells have another set of organelles not found in plant cells: lysosomes. The lysosomes are the cell's "garbage disposal." In plant cells, the digestive processes take place in vacuoles. Enzymes within the lysosomes aid the breakdown of proteins, polysaccharides, lipids, nucleic acids, and even worn-out organelles. These enzymes are active at a much lower pH than that of the cytoplasm. Therefore, the pH within lysosomes is more acidic than the pH of the cytoplasm. Many reactions that take place in the cytoplasm could not occur at a low pH, so the advantage of compartmentalizing the eukaryotic cell into organelles is apparent.

The Cell Wall

The cell wall is a rigid covering that protects the cell, provides structural support, and gives shape to the cell. Fungal and protistan cells also have cell walls. While the chief component of prokaryotic cell walls is peptidoglycan, the major organic molecule in the plant cell wall is cellulose, a polysaccharide comprised of glucose units. When you bite into a raw vegetable, like celery, it crunches. That's because you are tearing the rigid cell walls of the celery cells with your teeth.

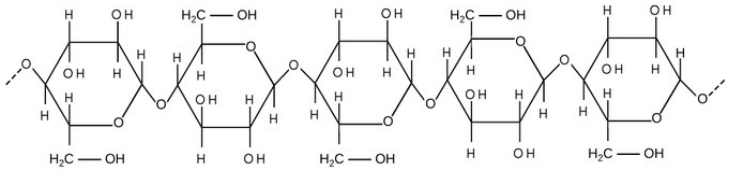


Figure: **Cellulose**: Cellulose is a long chain of β-glucose molecules connected by a 1-4 linkage. The dashed lines at each end of the figure indicate a series of many more glucose units. The size of the page makes it impossible to portray an entire cellulose molecule.

Chloroplasts

Like mitochondria, chloroplasts have their own DNA and ribosomes, but chloroplasts have an entirely different function. Chloroplasts are plant cell organelles that carry out photosynthesis. Photosynthesis is the series of reactions that use carbon dioxide, water, and light energy to make glucose and oxygen. This is a major difference between plants and animals; plants (autotrophs) are able to make their own food, like sugars, while animals (heterotrophs) must ingest their food.

Like mitochondria, chloroplasts have outer and inner membranes, but within the space enclosed by a chloroplast's inner membrane is a set of interconnected and stacked fluid-filled membrane sacs called thylakoids. Each stack of thylakoids is called a granum (plural = grana). The fluid enclosed by the inner membrane that surrounds the grana is called the stroma.

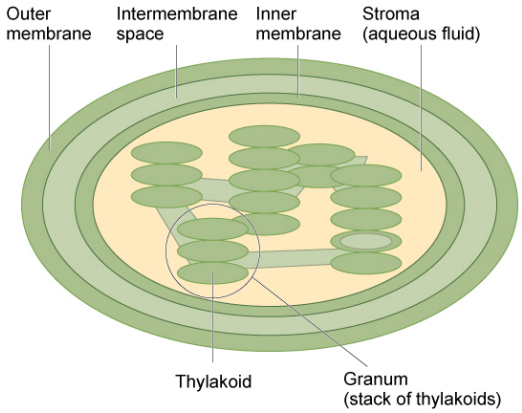


Figure: **The Chloroplast Structure**: The chloroplast has an outer membrane, an inner membrane, and membrane structures called thylakoids that are stacked into grana. The space inside the thylakoid membranes is called the thylakoid space. The light harvesting reactions take place in the thylakoid membranes, and the synthesis of sugar takes place in the fluid inside the inner membrane, which is called the stroma.

The chloroplasts contain a green pigment called chlorophyll, which captures the light energy that drives the reactions of photosynthesis. Like plant cells, photosynthetic protists also have chloroplasts. Some bacteria perform photosynthesis, but their chlorophyll is not relegated to an organelle.

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The Central Vacuole

The central vacuole plays a key role in regulating the cell's concentration of water in changing environmental conditions. When you forget to water a plant for a few days, it wilts. That's because as the water concentration in the soil becomes lower than the water concentration in the plant, water moves out of the central vacuoles and cytoplasm. As the central vacuole shrinks, it leaves the cell wall unsupported. This loss of support to the cell walls of plant cells results in the wilted appearance of the plant. The central vacuole also supports the expansion of the cell. When the central vacuole holds more water, the cell gets larger without having to invest a lot of energy in synthesizing new cytoplasm.

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4.7D: The Endoplasmic Reticulum

The endoplasmic reticulum is an organelle that is responsible for the synthesis of lipids and the modification of proteins.

Learning Objectives

- Describe the structure of the endoplasmic reticulum and its role in synthesis and metabolism

Key Points

- If the endoplasmic reticulum (ER) has ribosomes attached to it, it is called rough ER; if it does not, then it is called smooth ER.
- The proteins made by the rough endoplasmic reticulum are for use outside of the cell.
- Functions of the smooth endoplasmic reticulum include synthesis of carbohydrates, lipids, and steroid hormones; detoxification of medications and poisons; and storage of calcium ions.

Key Terms

- **lumen**: The cavity or channel within a tube or tubular organ.
- **reticulum**: A network

The Endoplasmic Reticulum

The endoplasmic reticulum (ER) is a series of interconnected membranous sacs and tubules that collectively modifies proteins and synthesizes lipids. However, these two functions are performed in separate areas of the ER: the rough ER and the smooth ER. The hollow portion of the ER tubules is called the lumen or cisternal space. The membrane of the ER, which is a phospholipid bilayer embedded with proteins, is continuous with the nuclear envelope.

Rough ER

The rough endoplasmic reticulum (RER) is so named because the ribosomes attached to its cytoplasmic surface give it a studded appearance when viewed through an electron microscope. Ribosomes transfer their newly synthesized proteins into the lumen of the RER where they undergo structural modifications, such as folding or the acquisition of side chains. These modified proteins will be incorporated into cellular membranes—the membrane of the ER or those of other organelles —or secreted from the cell (such as protein hormones, enzymes). The RER also makes phospholipids for cellular membranes. If the phospholipids or modified proteins are not destined to stay in the RER, they will reach their destinations via transport vesicles that bud from the RER's membrane. Since the RER is engaged in modifying proteins (such as enzymes, for example) that will be secreted from the cell, the RER is abundant in cells that secrete proteins. This is the case with cells of the liver, for example.

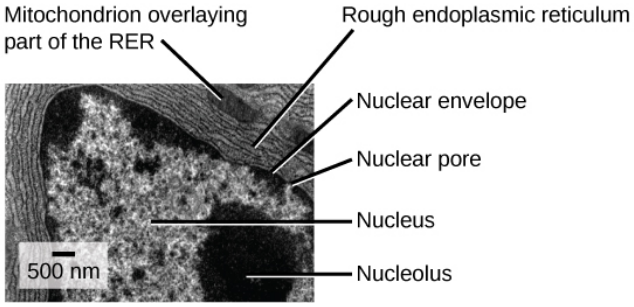

Figure: **Rough Endoplasmic Reticulum**: This transmission electron micrograph shows the rough endoplasmic reticulum and other organelles in a pancreatic cell.

Smooth ER

The smooth endoplasmic reticulum (SER) is continuous with the RER but has few or no ribosomes on its cytoplasmic surface. Functions of the SER include synthesis of carbohydrates, lipids, and steroid hormones; detoxification of medications and poisons; and storage of calcium ions. In muscle cells, a specialized SER called the sarcoplasmic reticulum is responsible for storage of the calcium ions that are needed to trigger the coordinated contractions of the muscle cells.

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4.7E: The Golgi Apparatus

Learning Objectives

- Describe the structure of the Golgi apparatus and its role in protein modification and secretion

We have already mentioned that vesicles can bud from the ER and transport their contents elsewhere, but where do the vesicles go? Before reaching their final destination, the lipids or proteins within the transport vesicles still need to be sorted, packaged, and tagged so that they wind up in the right place. Sorting, tagging, packaging, and distribution of lipids and proteins takes place in the Golgi apparatus (also called the Golgi body), a series of flattened membranes.

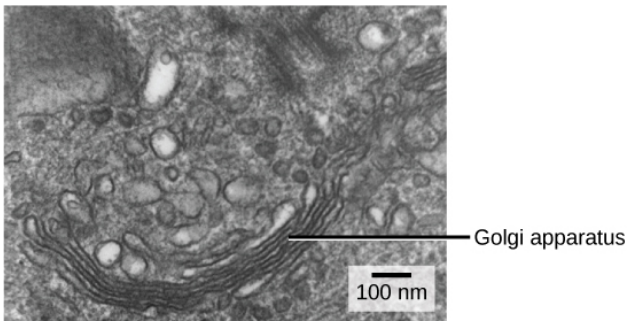

Figure: ***The Golgi apparatus sorts and packages cellular products****: The Golgi apparatus in this white blood cell is visible as a stack of semicircular, flattened rings in the lower portion of the image. Several vesicles can be seen near the Golgi apparatus.*

The receiving side of the Golgi apparatus is called the cis face. The opposite side is called the trans face. The transport vesicles that formed from the ER travel to the cis face, fuse with it, and empty their contents into the lumen of the Golgi apparatus. As the proteins and lipids travel through the Golgi, they undergo further modifications that allow them to be sorted. The most frequent modification is the addition of short chains of sugar molecules. These newly-modified proteins and lipids are then tagged with phosphate groups or other small molecules so that they can be routed to their proper destinations.

Finally, the modified and tagged proteins are packaged into secretory vesicles that bud from the trans face of the Golgi. While some of these vesicles deposit their contents into other parts of the cell where they will be used, other secretory vesicles fuse with the plasma membrane and release their contents outside the cell.

In another example of form following function, cells that engage in a great deal of secretory activity (such as cells of the salivary glands that secrete digestive enzymes or cells of the immune system that secrete antibodies) have an abundance of Golgi. In plant cells, the Golgi apparatus has the additional role of synthesizing polysaccharides, some of which are incorporated into the cell wall and some of which are used in other parts of the cell.

Key Points

- The Golgi apparatus is a series of flattened sacs that sort and package cellular materials.
- The Golgi apparatus has a cis face on the ER side and a trans face opposite of the ER.
- The *trans* face secretes the materials into vesicles, which then fuse with the cell membrane for release from the cell.

Key Terms

- **vesicle**: A membrane-bound compartment found in a cell.

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SECTION OVERVIEW

4.8: Other Eukaryotic Components

Topic hierarchy

4.8A: Peroxisomes

4.8B: Lysosomes

4.8C: Intermediate Filaments and Microtubules

4.8D: Extracellular Matrix of Animal Cells

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4.8A: Peroxisomes

Learning Objectives

- Name the various functions that peroxisomes perform inside the cell

A type of organelle found in both animal cells and plant cells, a peroxisome is a membrane-bound cellular organelle that contains mostly enzymes. Peroxisomes perform important functions, including lipid metabolism and chemical detoxification. They also carry out oxidation reactions that break down fatty acids and amino acids.

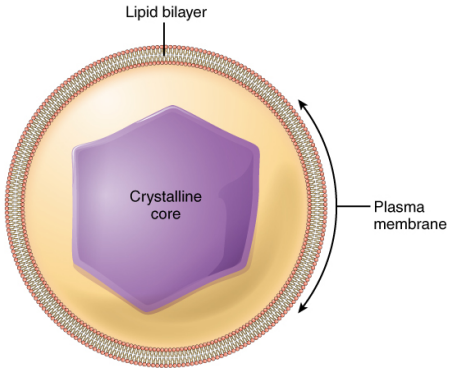

Figure: ***Peroxisomes****: Peroxisomes are membrane-bound organelles that contain an abundance of enzymes for detoxifying harmful substances and lipid metabolism.*

In contrast to the digestive enzymes found in lysosomes, the enzymes within peroxisomes serve to transfer hydrogen atoms from various molecules to oxygen, producing hydrogen peroxide (H_2O_2). In this way, peroxisomes neutralize poisons, such as alcohol, that enter the body. In order to appreciate the importance of peroxisomes, it is necessary to understand the concept of reactive oxygen species.

Reactive oxygen species (ROS), such as peroxides and free radicals, are the highly-reactive products of many normal cellular processes, including the mitochondrial reactions that produce ATP and oxygen metabolism. Examples of ROS include the hydroxyl radical OH, H_2O_2, and superoxide (O_{-2}). Some ROS are important for certain cellular functions, such as cell signaling processes and immune responses against foreign substances. Many ROS, however, are harmful to the body. Free radicals are reactive because they contain free unpaired electrons; they can easily oxidize other molecules throughout the cell, causing cellular damage and even cell death. Free radicals are thought to play a role in many destructive processes in the body, from cancer to coronary artery disease.

Peroxisomes oversee reactions that neutralize free radicals. They produce large amounts of the toxic H_2O_2 in the process, but contain enzymes that convert H_2O_2into water and oxygen. These by-products are then safely released into the cytoplasm. Like miniature sewage treatment plants, peroxisomes neutralize harmful toxins so that they do not cause damage in the cells. The liver is the organ primarily responsible for detoxifying the blood before it travels throughout the body; liver cells contain an exceptionally high number of peroxisomes.

Key Points

- Lipid metabolism and chemical detoxification are important functions of peroxisomes.
- Peroxisomes are responsible for oxidation reactions that break down fatty acids and amino acids.
- Peroxisomes oversee reactions that neutralize free radicals, which cause cellular damage and cell death.
- Peroxisomes chemically neutralize poisons through a process that produces large amounts of toxic H_2O_2, which is then converted into water and oxygen.
- The liver is the organ primarily responsible for detoxifying the blood before it travels throughout the body; as a result, liver cells contain large amounts of peroxisomes.

Key Terms

- **enzyme**: a globular protein that catalyses a biological chemical reaction
- **free radical**: Any molecule, ion or atom that has one or more unpaired electrons; they are generally highly reactive and often only occur as transient species.

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4.8B: Lysosomes

Learning Objectives

- Describe how lysosomes function as the cell's waste disposal system

Lysosomes are organelles that digest macromolecules, repair cell membranes, and respond to foreign substances entering the cell.

Lysosomes

A lysosome has three main functions: the breakdown/digestion of macromolecules (carbohydrates, lipids, proteins, and nucleic acids), cell membrane repairs, and responses against foreign substances such as bacteria, viruses and other antigens. When food is eaten or absorbed by the cell, the lysosome releases its enzymes to break down complex molecules including sugars and proteins into usable energy needed by the cell to survive. If no food is provided, the lysosome's enzymes digest other organelles within the cell in order to obtain the necessary nutrients.

In addition to their role as the digestive component and organelle-recycling facility of animal cells, lysosomes are considered to be parts of the endomembrane system. Lysosomes also use their hydrolytic enzymes to destroy pathogens (disease-causing organisms) that might enter the cell. A good example of this occurs in a group of white blood cells called macrophages, which are part of your body's immune system. In a process known as phagocytosis or endocytosis, a section of the plasma membrane of the macrophage invaginates (folds in) and engulfs a pathogen. The invaginated section, with the pathogen inside, then pinches itself off from the plasma membrane and becomes a vesicle. The vesicle fuses with a lysosome. The lysosome's hydrolytic enzymes then destroy the pathogen.

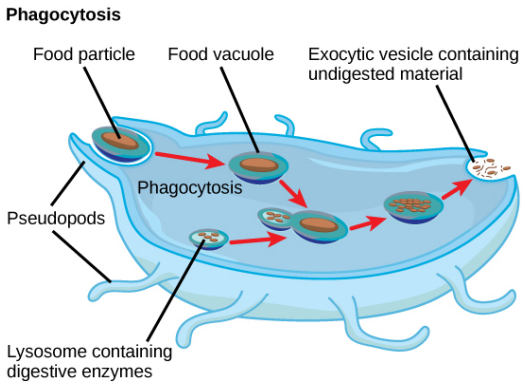

Figure: ***Lysosomes digest foreign substances that might harm the cell****: A macrophage has engulfed (phagocytized) a potentially pathogenic bacterium and then fuses with a lysosomes within the cell to destroy the pathogen. Other organelles are present in the cell but for simplicity are not shown.*

A lysosome is composed of lipids, which make up the membrane, and proteins, which make up the enzymes within the membrane. Usually, lysosomes are between 0.1 to 1.2µm, but the size varies based on the cell type. The general structure of a lysosome consists of a collection of enzymes surrounded by a single-layer membrane. The membrane is a crucial aspect of its structure because without it the enzymes within the lysosome that are used to breakdown foreign substances would leak out and digest the entire cell, causing it to die.

Lysosomes are found in nearly every animal-like eukaryotic cell. They are so common in animal cells because, when animal cells take in or absorb food, they need the enzymes found in lysosomes in order to digest and use the food for energy. On the other hand, lysosomes are not commonly-found in plant cells. Lysosomes are not needed in plant cells because they have cell walls that are tough enough to keep the large/foreign substances that lysosomes would usually digest out of the cell.

Key Points

- Lysosomes breakdown/digest macromolecules (carbohydrates, lipids, proteins, and nucleic acids), repair cell membranes, and respond against foreign substances such as bacteria, viruses and other antigens.
- Lysosomes contain enzymes that break down the macromolecules and foreign invaders.
- Lysosomes are composed of lipids and proteins, with a single membrane covering the internal enzymes to prevent the lysosome from digesting the cell itself.

- Lysosomes are found in all animal cells, but are rarely found within plant cells due to the tough cell wall surrounding a plant cell that keeps out foreign substances.

Key Terms

- **enzyme**: a globular protein that catalyses a biological chemical reaction
- **lysosome**: An organelle found in all types of animal cells which contains a large range of digestive enzymes capable of splitting most biological macromolecules.

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4.8C: Intermediate Filaments and Microtubules

Microtubules are part of the cell's cytoskeleton, helping the cell resist compression, move vesicles, and separate chromosomes at mitosis.

Learning Objectives

- Describe the roles of microtubules as part of the cell's cytoskeleton

Key Points

- Microtubules help the cell resist compression, provide a track along which vesicles can move throughout the cell, and are the components of cilia and flagella.
- Cilia and flagella are hair-like structures that assist with locomotion in some cells, as well as line various structures to trap particles.
- The structures of cilia and flagella are a "9+2 array," meaning that a ring of nine microtubules is surrounded by two more microtubules.
- Microtubules attach to replicated chromosomes during cell division and pull them apart to opposite ends of the pole, allowing the cell to divide with a complete set of chromosomes in each daughter cell.

Key Terms

- **microtubule**: Small tubes made of protein and found in cells; part of the cytoskeleton
- **flagellum**: a flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells
- **cytoskeleton**: A cellular structure like a skeleton, contained within the cytoplasm.

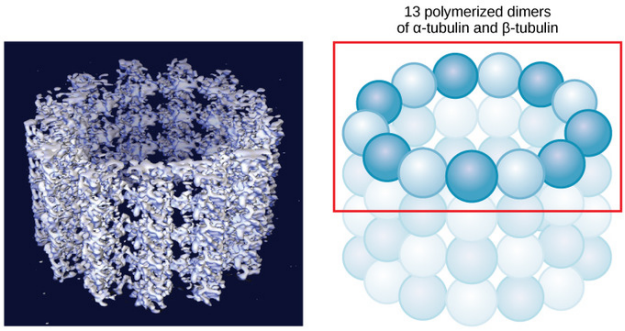

Figure: **Micrtubule Structure**: Microtubules are hollow, with walls consisting of 13 polymerized dimers of α-tubulin and β-tubulin (right image). The left image shows the molecular structure of the tube.

Microtubules

As their name implies, microtubules are small hollow tubes. Microtubules, along with microfilaments and intermediate filaments, come under the class of organelles known as the cytoskeleton. The cytoskeleton is the framework of the cell which forms the structural supporting component. Microtubules are the largest element of the cytoskeleton. The walls of the microtubule are made of polymerized dimers of α-tubulin and β-tubulin, two globular proteins. With a diameter of about 25 nm, microtubules are the widest components of the cytoskeleton. They help the cell resist compression, provide a track along which vesicles move through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. Like microfilaments, microtubules can dissolve and reform quickly.

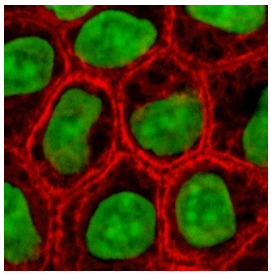

Figure: **Stained Keratin Intermediate filaments**: Keratin cytoskeletal intermediate filaments are concentrated around the edge of the cells and merge into the surface membrane. This network of intermediate filaments from cell to cell holds together tissues like skin.

Microtubules are also the structural elements of flagella, cilia, and centrioles (the latter are the two perpendicular bodies of the centrosome). In animal cells, the centrosome is the microtubule-organizing center. In eukaryotic cells, flagella and cilia are quite different structurally from their counterparts in prokaryotes.

Intermediate Filaments

Intermediate filaments (IFs) are cytoskeletal components found in animal cells. They are composed of a family of related proteins sharing common structural and sequence features. Intermediate filaments have an average diameter of 10 nanometers, which is between that of 7 nm actin (microfilaments), and that of 25 nm microtubules, although they were initially designated 'intermediate' because their average diameter is between those of narrower microfilaments (actin) and wider myosin filaments found in muscle cells. Intermediate filaments contribute to cellular structural elements and are often crucial in holding together tissues like skin.

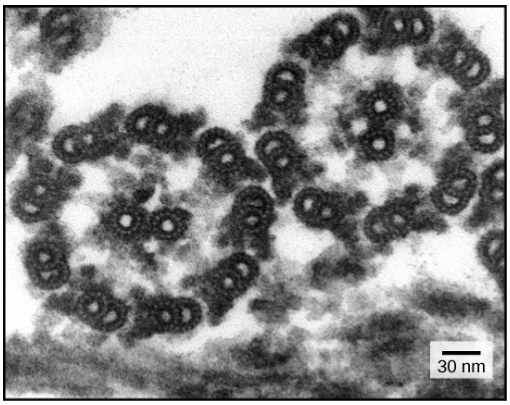

Figure: **Microtubules are the structural component of flagella**: This transmission electron micrograph of two flagella shows the 9 + 2 array of microtubules: nine microtubule doublets surround a single microtubule doublet.

Flagella and Cilia

Flagella (singular = flagellum) are long, hair-like structures that extend from the plasma membrane and are used to move an entire cell (for example, sperm, *Euglena*). When present, the cell has just one flagellum or a few flagella. When cilia (singular = cilium) are present, however, many of them extend along the entire surface of the plasma membrane. They are short, hair-like structures that are used to move entire cells (such as paramecia) or substances along the outer surface of the cell (for example, the cilia of cells lining the Fallopian tubes that move the ovum toward the uterus, or cilia lining the cells of the respiratory tract that trap particulate matter and move it toward your nostrils).

Despite their differences in length and number, flagella and cilia share a common structural arrangement of microtubules called a "9 + 2 array." This is an appropriate name because a single flagellum or cilium is made of a ring of nine microtubule doublets surrounding a single microtubule doublet in the center.

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4.8D: Extracellular Matrix of Animal Cells

The extracellular matrix of animal cells holds cells together to form a tissue and allow tissues to communicate with each other.

LEARNING OBJECTIVES

Explain the role of the extracellular matrix in animal cells

Key Takeaways

Key Points

- The extracellular matrix of animal cells is made up of proteins and carbohydrates.
- Cell communication within tissue and tissue formation are main functions of the extracellular matrix of animal cells.
- Tissue communication is kick-started when a molecule within the matrix binds a receptor; the end results are conformational changes that induce chemical signals that ultimately change activities within the cell.

Key Terms

- **collagen**: Any of more than 28 types of glycoprotein that forms elongated fibers, usually found in the extracellular matrix of connective tissue.
- **proteoglycan**: Any of many glycoproteins that have heteropolysaccharide side chains
- **extracellular matrix**: All the connective tissues and fibres that are not part of a cell, but rather provide support.

Extracellular Matrix of Animal Cells

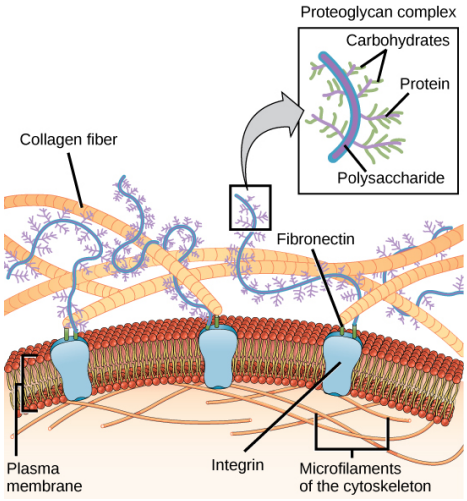

Figure: **The Extracellular Matrix**: The extracellular matrix consists of a network of proteins and carbohydrates.

Most animal cells release materials into the extracellular space. The primary components of these materials are proteins. Collagen is the most abundant of the proteins. Its fibers are interwoven with carbohydrate-containing protein molecules called proteoglycans. Collectively, these materials are called the extracellular matrix. Not only does the extracellular matrix hold the cells together to form a tissue, but it also allows the cells within the tissue to communicate with each other.

How does this cell communication occur? Cells have protein receptors on the extracellular surfaces of their plasma membranes. When a molecule within the matrix binds to the receptor, it changes the molecular structure of the receptor. The receptor, in turn, changes the conformation of the microfilaments positioned just inside the plasma membrane. These conformational changes induce chemical signals inside the cell that reach the nucleus and turn “on” or “off” the transcription of specific sections of DNA. This affects the production of associated proteins, thus changing the activities within the cell.

An example of the role of the extracellular matrix in cell communication can be seen in blood clotting. When the cells lining a blood vessel are damaged, they display a protein receptor called tissue factor. When a tissue factor binds with another factor in the extracellular matrix, it causes platelets to adhere to the wall of the damaged blood vessel and stimulates the adjacent smooth muscle cells in the blood vessel to contract (thus constricting the blood vessel). Subsequently, a series of steps are initiated which then prompt the platelets to produce clotting factors.

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SECTION OVERVIEW

4.9: Protein Export and Secretion

Topic hierarchy

4.9A: Endocytosis

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4.9A: Endocytosis

Learning Objectives

- Describe endocytosis, including phagocytosis, pinocytosis, and receptor-mediated endocytosis.

Endocytosis is a type of active transport that moves particles, such as large molecules, parts of cells, and even whole cells, into a cell. There are different variations of endocytosis, but all share a common characteristic: the plasma membrane of the cell invaginates, forming a pocket around the target particle. The pocket pinches off, resulting in the particle being contained in a newly-created intracellular vesicle formed from the plasma membrane.

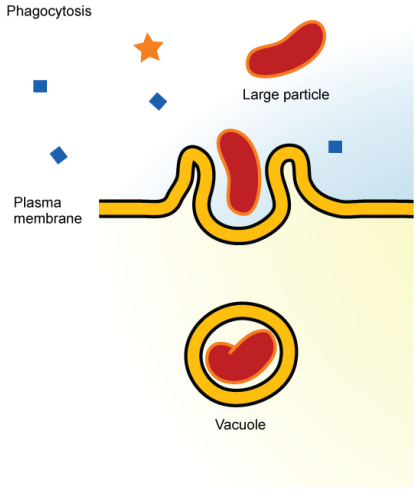

Figure: **Phagocytosis**: In phagocytosis, the cell membrane surrounds the particle and engulfs it.

Phagocytosis

Phagocytosis (the condition of “cell eating”) is the process by which large particles, such as cells or relatively large particles, are taken in by a cell. For example, when microorganisms invade the human body, a type of white blood cell called a neutrophil will remove the invaders through this process, surrounding and engulfing the microorganism, which is then destroyed by the neutrophil.

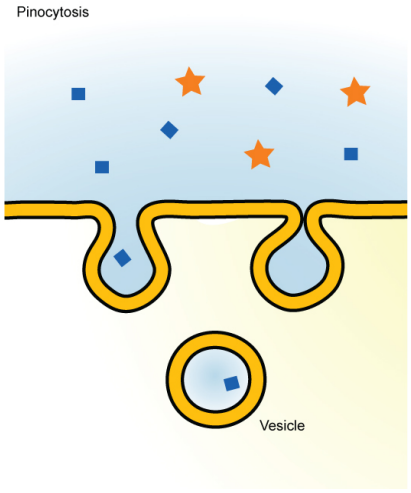

Figure: **Pinocytosis**: In pinocytosis, the cell membrane invaginates, surrounds a small volume of fluid, and pinches off.

In preparation for phagocytosis, a portion of the inward-facing surface of the plasma membrane becomes coated with a protein called clathrin, which stabilizes this section of the membrane. The coated portion of the membrane then extends from the body of the cell and surrounds the particle, eventually enclosing it. Once the vesicle containing the particle is enclosed within the cell, the clathrin disengages from the membrane and the vesicle merges with a lysosome for the breakdown of the material in the newly-formed compartment (endosome). When accessible nutrients from the degradation of the vesicular contents have been extracted,

the newly-formed endosome merges with the plasma membrane and releases its contents into the extracellular fluid. The endosomal membrane again becomes part of the plasma membrane.

Pinocytosis

A variation of endocytosis is called pinocytosis. This literally means “cell drinking” and was named at a time when the assumption was that the cell was purposefully taking in extracellular fluid. In reality, this is a process that takes in molecules, including water, which the cell needs from the extracellular fluid. Pinocytosis results in a much smaller vesicle than does phagocytosis, and the vesicle does not need to merge with a lysosome.

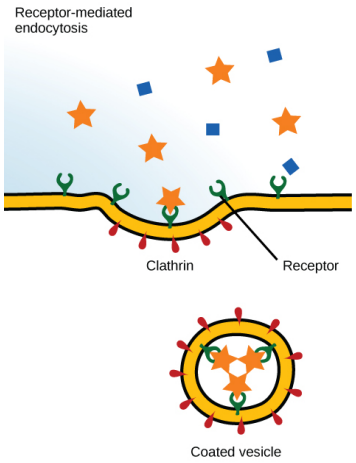

Figure: **Receptor-Mediated Endocytosis**: In receptor-mediated endocytosis, uptake of substances by the cell is targeted to a single type of substance that binds to the receptor on the external surface of the cell membrane.

Potocytosis, a variant of pinocytosis, is a process that uses a coating protein, called caveolin, on the cytoplasmic side of the plasma membrane, which performs a similar function to clathrin. The cavities in the plasma membrane that form the vacuoles have membrane receptors and lipid rafts in addition to caveolin. The vacuoles or vesicles formed in caveolae (singular caveola) are smaller than those in pinocytosis. Potocytosis is used to bring small molecules into the cell and to transport these molecules through the cell for their release on the other side of the cell, a process called transcytosis.

Receptor-mediated Endocytosis

A targeted variation of endocytosis, known as receptor-mediated endocytosis, employs receptor proteins in the plasma membrane that have a specific binding affinity for certain substances. In receptor-mediated endocytosis, as in phagocytosis, clathrin is attached to the cytoplasmic side of the plasma membrane. If uptake of a compound is dependent on receptor-mediated endocytosis and the process is ineffective, the material will not be removed from the tissue fluids or blood. Instead, it will stay in those fluids and increase in concentration. Some human diseases are caused by the failure of receptor-mediated endocytosis. For example, the form of cholesterol termed low-density lipoprotein or LDL (also referred to as “bad” cholesterol) is removed from the blood by receptor-mediated endocytosis. In the human genetic disease familial hypercholesterolemia, the LDL receptors are defective or missing entirely. People with this condition have life-threatening levels of cholesterol in their blood, because their cells cannot clear LDL particles from their blood.

Although receptor-mediated endocytosis is designed to bring specific substances that are normally found in the extracellular fluid into the cell, other substances may gain entry into the cell at the same site. Flu viruses, diphtheria, and cholera toxin all have sites that cross-react with normal receptor-binding sites and gain entry into cells.

Key Points

- Endocytosis consists of phagocytosis, pinocytosis, and receptor -mediated endocytosis.
- Endocytosis takes particles into the cell that are too large to passively cross the cell membrane.
- Phagocytosis is the taking in of large food particles, while pinocytosis takes in liquid particles.
- Receptor-mediated endocytosis uses special receptor proteins to help carry large particles across the cell membrane.

Key Terms

- **endosome**: An endocytic vacuole through which molecules internalized during endocytosis pass en route to lysosomes
- **neutrophil**: A cell, especially a white blood cell that consumes foreign invaders in the blood.

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SECTION OVERVIEW

4. 10: Studying Cells

Topic hierarchy

4.10A: Microscopy

4.10B: Crystallographic Analysis

4.10C: Genetic Analysis

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CHAPTER OVERVIEW

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  - 5.1B: Chemoautotrophs and Chemohetrotrophs
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Thumbnail: The Krebs cycle, also known as the citric acid cycle, is summarized here. Note incoming two-carbon acetyl results in the main outputs per turn of two CO_2, three NADH, one $FADH_2$, and one ATP (or GTP) molecules made by substrate-level phosphorylation. Two turns of the Krebs cycle are required to process all of the carbon from one glucose molecule.

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SECTION OVERVIEW

5.1: Types of Metabolism

Topic hierarchy

5.1A: Photoautotrophs and Photohetrotrophs

5.1B: Chemoautotrophs and Chemohetrotrophs

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5.1A: Photoautotrophs and Photohetrotrophs

Learning Objectives

- Differentiate photoautotrophs from photoheterotrophs

Phototrophs are organisms that use light as their source of energy to produce ATP and carry out various cellular processes. Not all phototrophs are photosynthetic but they all constitute a food source for heterotrophic organisms. All phototrophs either use electron transport chain or direct proton pumping to establish an electro-chemical gradient utilized by ATP synthase to provide molecular energy for the cell. Phototrophs can be of two types based on their metabolism.

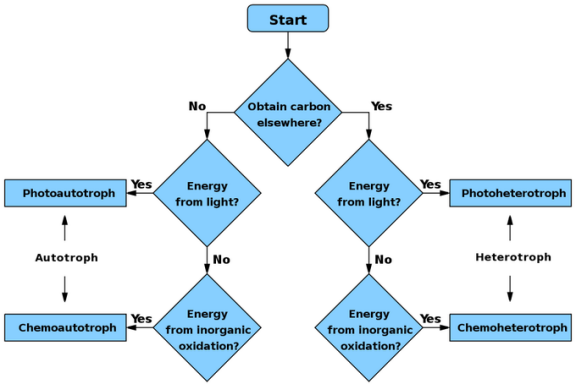

Figure: **Types of microbial metabolism**: Flowchart summarizing the types of microbial metabolism.

Photoautotrophs

An autotroph is an organism able to make its own food. Photoautotrophs are organisms that carry out photosynthesis. Using energy from sunlight, carbon dioxide and water are converted into organic materials to be used in cellular functions such as biosynthesis and respiration. In an ecological context, they provide nutrition for all other forms of life (besides other autotrophs such as chemotrophs). In terrestrial environments plants are the predominant variety, while aquatic environments include a range of phototrophic organisms such as algae, protists, and bacteria. In photosynthetic bacteria and cyanobacteria that build up carbon dioxide and water into organic cell materials using energy from sunlight, starch is produced as final product. This process is an essential storage form of carbon, which can be used when light conditions are too poor to satisfy the immediate needs of the organism.

Photoheterotrophs

A heterotroph is an organism that depends on organic matter already produced by other organisms for its nourishment. Photoheterotrophs obtain their energy from sunlight and carbon from organic material and not carbon dioxide. Most of the well-recognized phototrophs are autotrophs, also known as photoautotrophs, and can fix carbon. They can be contrasted with chemotrophs that obtain their energy by the oxidation of electron donors in their environments. Photoheterotrophs produce ATP through photophosphorylation but use environmentally obtained organic compounds to build structures and other bio-molecules. Photoautotrophic organisms are sometimes referred to as holophytic.

Key Points

- Phototrophs are organisms that carry out photon capture to acquire energy.
- Photoautotrophs convert inorganic materials into organic materials for use in cellular functions such as biosynthesis and respiration and provide nutrition for many other forms of life.
- Photoheterotrophs depend on light for their source of energy and mostly organic compounds from the environment for their source of carbon.

Key Terms

- **ATP synthase**: an important enzyme that catalyzes the conversion of adenosine diphosphate into adenosine triphosphate.
- **photosynthesis**: The process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts.

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5.1B: Chemoautotrophs and Chemohetrotrophs

Learning Objectives

- Compare chemoautotrophs and chemoheterotrophs

Chemotrophs are a class of organisms that obtain their energy through the oxidation of inorganic molecules, such as iron and magnesium. The most common type of chemotrophic organisms are prokaryotic and include both bacteria and fungi. All of these organisms require carbon to survive and reproduce. The ability of chemotrophs to produce their own organic or carbon-containing molecules differentiates these organisms into two different classifications–chemoautotrophs and chemoheterotrophs.

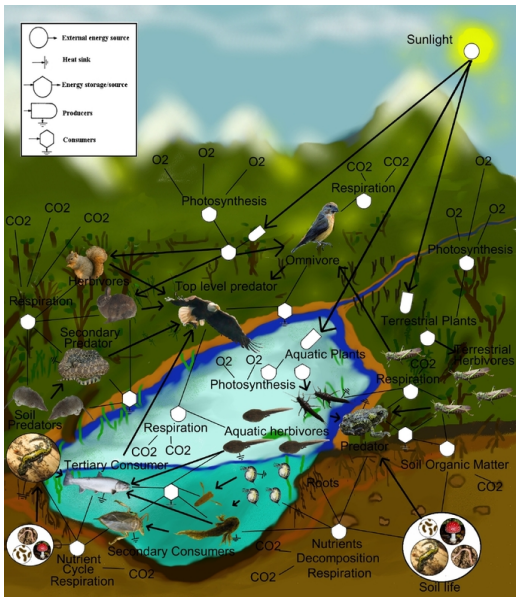

Figure: **Organismal and environmental interactions in a wetland**: sources of energy and carbon for each trophic level.

Chemoautotrophs

Chemoautotrophs are able to synthesize their own organic molecules from the fixation of carbon dioxide. These organisms are able to produce their own source of food, or energy. The energy required for this process comes from the oxidation of inorganic molecules such as iron, sulfur or magnesium. Chemoautotrophs are able to thrive in very harsh environments, such as deep sea vents, due to their lack of dependence on outside sources of carbon other than carbon dioxide. Chemoautotrophs include nitrogen fixing bacteria located in the soil, iron oxidizing bacteria located in the lava beds, and sulfur oxidizing bacteria located in deep sea thermal vents.

Chemoheterotrophs

Chemoheterotrophs, unlike chemoautotrophs, are unable to synthesize their own organic molecules. Instead, these organisms must ingest preformed carbon molecules, such as carbohydrates and lipids, synthesized by other organisms. They do, however, still obtain energy from the oxidation of inorganic molecules like the chemoautotrophs. Chemoheterotrophs are only able to thrive in environments that are capable of sustaining other forms of life due to their dependence on these organisms for carbon sources. Chemoheterotrophs are the most abundant type of chemotrophic organisms and include most bacteria, fungi and protozoa.

Key Points

- Chemotrophs are organisms that obtain energy by the oxidation of electron donors in their environment.
- Chemoautotrophs use inorganic energy sources to synthesize organic compounds from carbon dioxide.
- Chemoheterotrophs are unable to utilize carbon dioxide to form their own organic compounds. Their carbon source is rather derived from sulfur, carbohydrates, lipids, and proteins.

Key Terms

- **inorganic molecule**: lacks carbon and hydrogen atoms.

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SECTION OVERVIEW

5.2: Energy Production

Topic hierarchy

5.2A: Control of Catabolic Pathways

5.2B: Transforming Chemical Energy

5.2C: Connecting Other Sugars to Glucose Metabolism

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5.2A: Control of Catabolic Pathways

Learning Objectives

- Explain how catabolic pathways are controlled

Enzymes, proteins, electron carriers, and pumps that play roles in glycolysis, the citric acid cycle, and the electron transport chain tend to catalyze non-reversible reactions. In other words, if the initial reaction takes place, the pathway is committed to proceeding with the remaining reactions. Whether a particular enzyme activity is released depends upon the energy needs of the cell (as reflected by the levels of ATP, ADP, and AMP).

Glycolysis

The control of glycolysis begins with the first enzyme in the pathway, hexokinase. This enzyme catalyzes the phosphorylation of glucose, which helps to prepare the compound for cleavage in a later step. The presence of the negatively-charged phosphate in the molecule also prevents the sugar from leaving the cell. When hexokinase is inhibited, glucose diffuses out of the cell and does not become a substrate for the respiration pathways in that tissue. The product of the hexokinase reaction is glucose-6-phosphate, which accumulates when a later enzyme, phosphofructokinase, is inhibited.

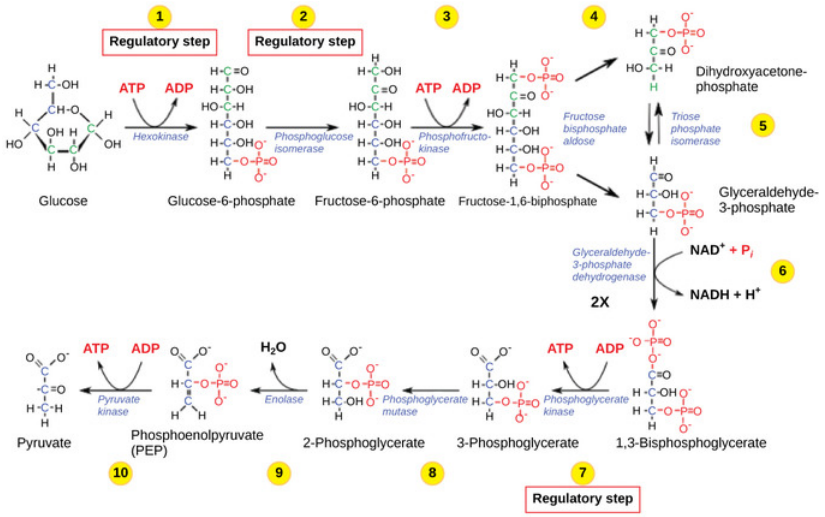

Figure: **Glycolysis**: The glycolysis pathway is primarily regulated at the three key enzymatic steps (1, 2, and 7) as indicated. Note that the first two steps that are regulated occur early in the pathway and involve hydrolysis of ATP.

Phosphofructokinase is the main enzyme controlled in glycolysis. High levels of ATP, citrate, or a lower, more acidic pH decrease the enzyme's activity. An increase in citrate concentration can occur because of a blockage in the citric acid cycle. Fermentation, with its production of organic acids like lactic acid, frequently accounts for the increased acidity in a cell; however, the products of fermentation do not typically accumulate in cells.

The last step in glycolysis is catalyzed by pyruvate kinase. The pyruvate produced can proceed to be catabolized or converted into the amino acid alanine. If no more energy is needed and alanine is in adequate supply, the enzyme is inhibited. The enzyme's activity is increased when fructose-1,6-bisphosphate levels increase. (Recall that fructose-1,6-bisphosphate is an intermediate in the first half of glycolysis.) The regulation of pyruvate kinase involves phosphorylation, resulting in a less-active enzyme. Dephosphorylation by a phosphatase reactivates it. Pyruvate kinase is also regulated by ATP (a negative allosteric effect).

If more energy is needed, more pyruvate will be converted into acetyl CoA through the action of pyruvate dehydrogenase. If either acetyl groups or NADH accumulate, there is less need for the reaction and the rate decreases. Pyruvate dehydrogenase is also regulated by phosphorylation: a kinase phosphorylates it to form an inactive enzyme, and a phosphatase reactivates it. The kinase and the phosphatase are also regulated.

Citric Acid Cycle

The citric acid cycle is controlled through the enzymes that catalyze the reactions that make the first two molecules of NADH. These enzymes are isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. When adequate ATP and NADH levels are

available, the rates of these reactions decrease. When more ATP is needed, as reflected in rising ADP levels, the rate increases. α-Ketoglutarate dehydrogenase will also be affected by the levels of succinyl CoA, a subsequent intermediate in the cycle, causing a decrease in activity. A decrease in the rate of operation of the pathway at this point is not necessarily negative as the increased levels of the α-ketoglutarate not used by the citric acid cycle can be used by the cell for amino acid (glutamate) synthesis.

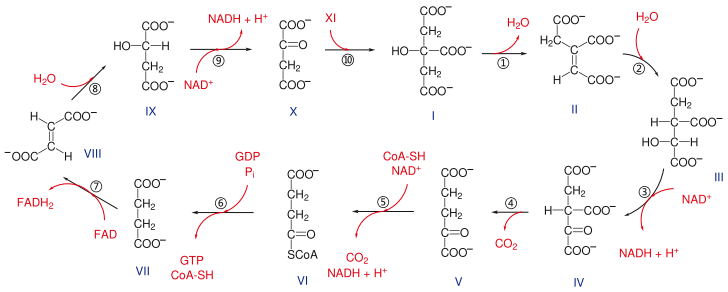

Figure: **Citric Acid Cycle**: Enzymes, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase, catalyze the reactions that make the first two molecules of NADH in the citric acid cycle. Rates of the reaction decrease when sufficient ATP and NADH levels are reached.

Electron Transport Chain

Specific enzymes of the electron transport chain are unaffected by feedback inhibition, but the rate of electron transport through the pathway is affected by the levels of ADP and ATP. Greater ATP consumption by a cell is indicated by a buildup of ADP. As ATP usage decreases, the concentration of ADP decreases: ATP begins to build up in the cell. This change in the relative concentration of ADP to ATP triggers the cell to slow down the electron transport chain.

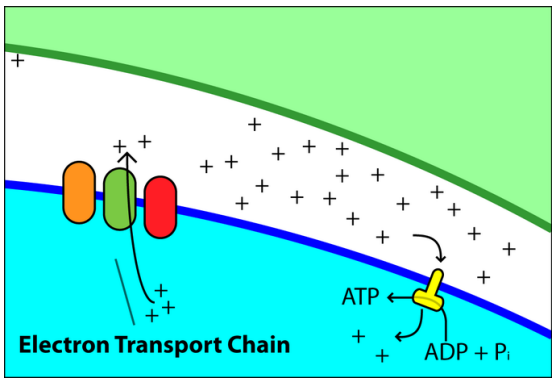

Figure: **Electron Chain Transport**: Levels of ADP and ATP affect the rate of electron transport through this type of chain transport.

Key Points

- Glycolysis, the citric acid cycle, and the electron transport chain are catabolic pathways that bring forth non-reversible reactions.
- Glycolysis control begins with hexokinase, which catalyzes the phosphorylation of glucose; its product is glucose-6- phosphate, which accumulates when phosphofructokinase is inhibited.
- The citric acid cycle is controlled through the enzymes that break down the reactions that make the first two molecules of NADH.
- The rate of electron transport through the electron transport chain is affected by the levels of ADP and ATP, whereas specific enzymes of the electron transport chain are unaffected by feedback inhibition.

Key Terms

- **phosphofructokinase**: any of a group of kinase enzymes that convert fructose phosphates to biphosphate
- **glycolysis**: the cellular metabolic pathway of the simple sugar glucose to yield pyruvic acid and ATP as an energy source
- **kinase**: any of a group of enzymes that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific target molecules (substrates); the process is termed phosphorylation

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5.2B: Transforming Chemical Energy

Learning Objectives

- Discuss the importance of cellular respiration

Introduction: Cellular Respiration

An electrical energy plant converts energy from one form to another form that can be more easily used. For example, geothermal energy plants start with underground thermal energy (heat) and transform it into electrical energy that will be transported to homes and factories.



Figure: **Energy Plant**: This geothermal energy plant transforms thermal energy from deep in the ground into electrical energy, which can be easily used.

Like a generating plant, living organisms must take in energy from their environment and convert it into to a form their cells can use. Organisms ingest large molecules, like carbohydrates, proteins, and fats, and convert them into smaller molecules like carbon dioxide and water. This process is called cellular respiration, a form of catabolism, and makes energy available for the cell to use. The energy released by cellular respiration is temporarily captured by the formation of adenosine triphosphate (ATP) within the cell. ATP is the principle form of stored energy used for cellular functions and is frequently referred to as the energy currency of the cell.

The nutrients broken down through cellular respiration lose electrons throughout the process and are said to be oxidized. When oxygen is used to help drive the oxidation of nutrients the process is called aerobic respiration. Aerobic respiration is common among the eukaryotes, including humans, and takes place mostly within the mitochondria. Respiration occurs within the cytoplasm of prokaryotes. Several prokaryotes and a few eukaryotes use an inorganic molecule other than oxygen to drive the oxidation of their nutrients in a process called anaerobic respiration. Electron acceptors for anaerobic respiration include nitrate, sulfate, carbon dioxide, and several metal ions.

The energy released during cellular respiration is then used in other biological processes. These processes build larger molecules that are essential to an organism's survival, such as amino acids, DNA, and proteins. Because they synthesize new molecules, these processes are examples of anabolism.

Key Points

- Organisms ingest organic molecules like the carbohydrate glucose to obtain the energy needed for cellular functions.
- The energy in glucose can be extracted in a series of chemical reactions known as cellular respiration.
- Cellular respiration produces energy in the form of ATP, which is the universal energy currency for cells.

Key Terms

- **aerobic respiration**: the process of converting the biochemical energy in nutrients to ATP in the presence of oxygen
- **adenosine triphosphate**: a multifunctional nucleoside triphosphate used in cells as a coenzyme, often called the "molecular unit of energy currency" in intracellular energy transfer
- **cellular respiration**: the set of the metabolic reactions and processes that take place in the cells of organisms to convert biochemical energy from nutrients into adenosine triphosphate (ATP)
- **catabolism**: the breakdown of large molecules into smaller ones usually accompanied by the release of energy

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5.2C: Connecting Other Sugars to Glucose Metabolism

Learning Objectives

- Identify the types of sugars involved in glucose metabolism

You have learned about the catabolism of glucose, which provides energy to living cells. But living things consume more than glucose for food. How does a turkey sandwich end up as ATP in your cells? This happens because all of the catabolic pathways for carbohydrates, proteins, and lipids eventually connect into glycolysis and the citric acid cycle pathways.

Metabolic pathways should be thought of as porous; that is, substances enter from other pathways, and intermediates leave for other pathways. These pathways are not closed systems. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways. Like sugars and amino acids, the catabolic pathways of lipids are also connected to the glucose catabolism pathways.

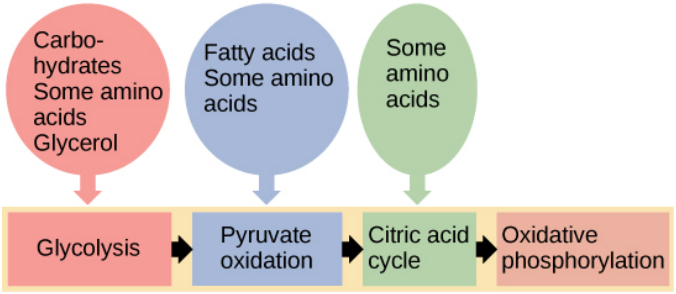

Figure: **Glycogen Pathway**: Glycogen from the liver and muscles, hydrolyzed into glucose-1-phosphate, together with fats and proteins, can feed into the catabolic pathways for carbohydrates.

Glycogen, a polymer of glucose, is an energy-storage molecule in animals. When there is adequate ATP present, excess glucose is shunted into glycogen for storage. Glycogen is made and stored in both the liver and muscles. The glycogen is hydrolyzed into the glucose monomer, glucose-1-phosphate (G-1-P), if blood sugar levels drop. The presence of glycogen as a source of glucose allows ATP to be produced for a longer period of time during exercise. Glycogen is broken down into G-1-P and converted into glucose-6-phosphate (G-6-P) in both muscle and liver cells; this product enters the glycolytic pathway.

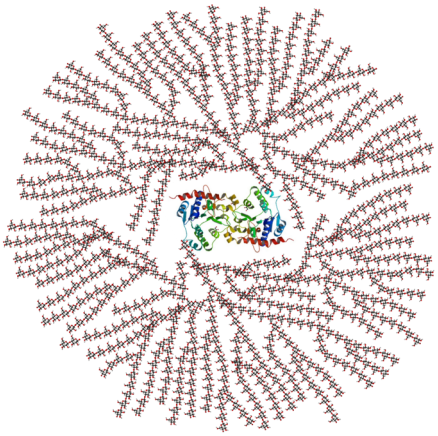

Figure: **Glycogen Structure**: Schematic two-dimensional cross-sectional view of glycogen: A core protein of glycogenin is surrounded by branches of glucose units. The entire globular granule may contain around 30,000 glucose units.

Galactose is the sugar in milk. Infants have an enzyme in the small intestine that metabolizes lactose to galactose and glucose. In areas where milk products are regularly consumed, adults have also evolved this enzyme. Galactose is converted in the liver to G-6-P and can thus enter the glycolytic pathway.

Fructose is one of the three dietary monosaccharides (along with glucose and galactose) which are absorbed directly into the bloodstream during digestion. Fructose is absorbed from the small intestine and then passes to the liver to be metabolized, primarily to glycogen. The catabolism of both fructose and galactose produces the same number of ATP molecules as glucose.

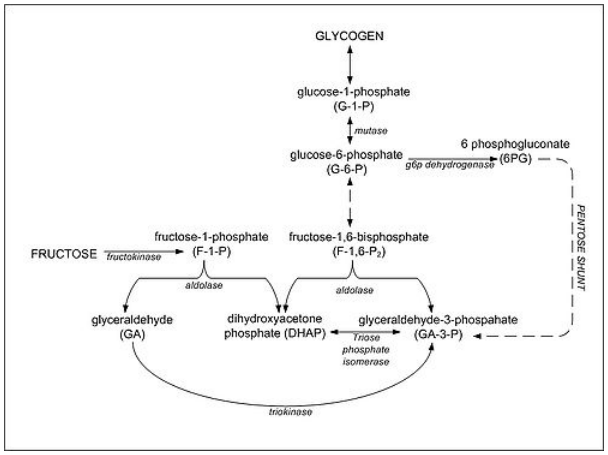

Figure: **Fructose Metabolism**: Although the metabolism of fructose and glucose share many of the same intermediate structures, they have very different metabolic fates in human metabolism.

Sucrose is a disaccharide with a molecule of glucose and a molecule of fructose bonded together with a glycosidic linkage. The catabolism of sucrose breaks it down to monomers of glucose and fructose. The glucose can directly enter the glycolytic pathway while fructose must first be converted to glycogen, which can be broken down to G-1-P and enter the glycolytic pathway as described above.

Key Points

- When blood sugar levels drop, glycogen is broken down into glucose -1-phosphate, which is then converted to glucose-6-phosphate and enters glycolysis for ATP production.
- In the liver, galactose is converted to glucose-6-phosphate in order to enter the glycolytic pathway.
- Fructose is converted into glycogen in the liver and then follows the same pathway as glycogen to enter glycolysis.
- Sucrose is broken down into glucose and fructose; glucose enters the pathway directly while fructose is converted to glycogen.

Key Terms

- **disaccharide**: A sugar, such as sucrose, maltose, or lactose, consisting of two monosaccharides combined together.
- **glycogen**: A polysaccharide that is the main form of carbohydrate storage in animals; converted to glucose as needed.
- **monosaccharide**: A simple sugar such as glucose, fructose, or deoxyribose that has a single ring.

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SECTION OVERVIEW

5.3: Catabolism

Topic hierarchy

5.3A: Types of Catabolism

5.3B: Pyruvic Acid and Metabolism

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5.3A: Types of Catabolism

Learning Objectives

- Summarize various types of catabolism included in metabolism (catabolism of carbohydrates, proteins and fats)

Catabolism is the set of metabolic processes that break down large molecules. These include breaking down and oxidizing food molecules. The purpose of catabolic reactions is to provide the energy and components needed by anabolic reactions. The exact nature of these catabolic reactions differ from organism to organism; organisms can be classified based on their sources of energy and carbon, their primary nutritional groups. Organic molecules are used as a source of energy by organotrophs, while lithotrophs use inorganic substrates and phototrophs capture sunlight as chemical energy.

All these different forms of metabolism depend on redox reactions that involve the transfer of electrons from reduced donor molecules such as organic molecules, water, ammonia, hydrogen sulfide or ferrous ions to acceptor molecules such as oxygen, nitrate or sulfate. In animals these reactions involve complex organic molecules being broken down to simpler molecules, such as carbon dioxide and water. In photosynthetic organisms such as plants and cyanobacteria, these electron-transfer reactions do not release energy, but are used as a way of storing energy absorbed from sunlight.

The most common set of catabolic reactions in animals can be separated into three main stages. In the first, large organic molecules such as proteins, polysaccharides, or lipids are digested into their smaller components outside cells. Next, these smaller molecules are taken up by cells and converted to yet smaller molecules, usually the acetyl coenzyme *A (acetyl-CoA)*, which releases some energy. Finally, the acetyl group on the CoA is oxidized to water and carbon dioxide in the citric acid cycle and electron transport chain, releasing the energy that is stored by reducing the coenzyme nicotinamide adenine dinucleotide (NAD+) into NADH.

Macromolecules such as starch, cellulose or proteins cannot be rapidly taken up by cells and must be broken into their smaller units before they can be used in cell metabolism. Several common classes of enzymes digest these polymers. These digestive enzymes include proteases that digest proteins into amino acids, as well as glycoside hydrolases that digest polysaccharides into monosaccharides. Microbes secrete digestive enzymes into their surroundings, while animals only secrete these enzymes from specialized cells in their guts. The amino acids or sugars released by these extracellular enzymes are then pumped into cells by specific active transport proteins. A simplified schematic of the catabolism of carbohydrates, proteins and fats is shown in.

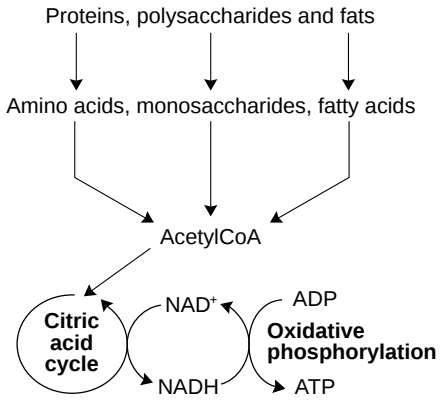

Figure: **Catabolism**: A simplified outline of the catabolism of proteins, carbohydrates and fats

Carbohydrate Catabolism

Carbohydrate catabolism is the breakdown of carbohydrates into smaller units. Carbohydrates are usually taken into cells once they have been digested into monosaccharides. Once inside, the major route of breakdown is glycolysis, where sugars such as glucose and fructose are converted into pyruvate and some ATP is generated. Pyruvate is an intermediate in several metabolic pathways, but the majority is converted to acetyl-CoA and fed into the citric acid cycle. Although some more ATP is generated in the citric acid cycle, the most important product is NADH, which is made from NAD+ as the acetyl-CoA is oxidized. This oxidation releases carbon dioxide as a waste product. In anaerobic conditions, glycolysis produces lactate, through the enzyme lactate dehydrogenase re-oxidizing NADH to NAD+ for re-use in glycolysis.

The Pentose Phosphate Pathway

An alternative route for glucose breakdown is the pentose phosphate pathway, which reduces the coenzyme NADPH and produces pentose sugars such as ribose, the sugar component of nucleic acids. Fats are catabolised by hydrolysis to free fatty acids and glycerol. The glycerol initiates glycolysis and the fatty acids are broken down by beta oxidation to release acetyl-CoA, which then is fed into the citric acid cycle. Fatty acids release more energy upon oxidation than carbohydrates because carbohydrates contain more oxygen in their structures.

Amino acids are either used to synthesize proteins and other biomolecules, or oxidized to urea and carbon dioxide as a source of energy. The oxidation pathway starts with the removal of the amino group by a transaminase. The amino group is fed into the urea cycle, leaving a deaminated carbon skeleton in the form of a keto acid. Several of these keto acids are intermediates in the citric acid cycle, for example the deamination of glutamate forms α-ketoglutarate. The glucogenic amino acids can also be converted into glucose, through gluconeogenesis.

Key Points

- The purpose of the catabolic reactions is to provide the energy and components needed by anabolic reactions.
- Microbes simply secrete digestive enzymes into their surroundings, while animals only secrete these enzymes from specialized cells in their guts.
- Fats are catabolised by hydrolysis to free fatty acids and glycerol.
- Amino acids are either used to synthesize proteins and other biomolecules, or oxidized to urea and carbon dioxide as a source of energy.
- Carbohydrates are usually taken into cells once they have been digested into monosaccharides and then processed inside the cell via glycolysis.

Key Terms

- **polymer**: A long or larger molecule consisting of a chain or network of many repeating units, formed by chemically bonding together many identical or similar small molecules called monomers. A polymer is formed by polymerization, the joining of many monomer molecules.
- **acetyl CoA**: Acetyl coenzyme A or acetyl-CoA is an important molecule in metabolism, used in many biochemical reactions. Its main function is to convey the carbon atoms within the acetyl group to the citric acid cycle (Krebs cycle) to be oxidized for energy production.
- **catabolism**: Destructive metabolism, usually includes the release of energy and breakdown of materials.

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5.3B: Pyruvic Acid and Metabolism

Learning Objectives

- Outline the metabolic processes that involve pyruvate

Pyruvic acid ($CH_3COCOOH$; is an organic acid, a ketone, and the simplest of the alpha-keto acids. The carboxylate (COO^-) anion of pyruvic acid. The Brønsted–Lowry conjugate base, CH_3COCOO^-, is known as pyruvate, and is a key intersection in several metabolic pathways.

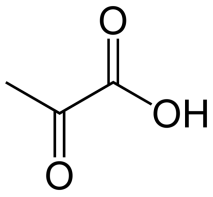

Figure: ***Pyruvic acid****: Pyruvic acid can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through acetyl-CoA. It can also be used to construct the amino acid alanine and be converted into ethanol. Pyruvic acid supplies energy to living cells through the citric acid cycle (also known as the Krebs cycle) when oxygen is present (aerobic respiration), and alternatively ferments to produce lactic acid when oxygen is lacking (fermentation).*

Pyruvic acid can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through acetyl-CoA. It can also be used to construct the amino acid alanine, and it can be converted into ethanol.

Pyruvic acid supplies energy to living cells through the citric acid cycle (also known as the Krebs cycle) when oxygen is present (aerobic respiration); when oxygen is lacking, it ferments to produce lactic acid. Pyruvate is an important chemical compound in biochemistry. It is the output of the anaerobic metabolism of glucose known as glycolysis. One molecule of glucose breaks down into two molecules of pyruvate, which are then used to provide further energy in one of two ways. Pyruvate is converted into acetyl- coenzyme A, which is the main input for a series of reactions known as the Krebs cycle. Pyruvate is also converted to oxaloacetate by an anaplerotic reaction, which replenishes Krebs cycle intermediates; also, oxaloacetate is used for gluconeogenesis. These reactions are named after Hans Adolf Krebs, the biochemist awarded the 1953 Nobel Prize for physiology, jointly with Fritz Lipmann, for research into metabolic processes. The cycle is also known as the citric acid cycle or tri-carboxylic acid cycle, because citric acid is one of the intermediate compounds formed during the reactions.

If insufficient oxygen is available, the acid is broken down anaerobically, creating lactate in animals and ethanol in plants and microorganisms. Pyruvate from glycolysis is converted by fermentation to lactate using the enzyme lactate dehydrogenase and the coenzyme NADH in lactate fermentation. Alternatively it is converted to acetaldehyde and then to ethanol in alcoholic fermentation.

Pyruvate is a key intersection in the network of metabolic pathways. Pyruvate can be converted into carbohydrates via gluconeogenesis, to fatty acids or energy through acetyl-CoA, to the amino acid alanine, and to ethanol. Therefore, it unites several key metabolic processes.

Key Points

- Pyruvic acid can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through acetyl-CoA.
- Pyruvic acid supplies energy to living cells through the citric acid cycle (also known as the Krebs cycle) when oxygen is present (aerobic respiration); it ferments to produce lactic acid when oxygen is lacking (fermentation).
- Pyruvate is the output of the anaerobic metabolism of glucose known as glycolysis.
- Pyruvate can be converted into carbohydrates via gluconeogenesis, to fatty acids or energy through acetyl-CoA, to the amino acid alanine, and to ethanol.

Key Terms

- **pyruvic acid**: A colourless liquid; an important intermediate in the metabolism of proteins and carbohydrates, and in fermentation.

- **conjugate base**: Any compound, of general formula Xn+, which can be transformed into a conjugate acid HX(n+1)+ by the gain of a proton.
- **Krebs cycle**: A series of enzymatic reactions that occurs in all aerobic organisms; it involves the oxidative metabolism of acetyl units and serves as the main source of cellular energy.

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SECTION OVERVIEW

5.4: Glycolysis

Topic hierarchy

5.4A: Importance of Glycolysis

5.4B: Electron Donors and Acceptors

5.4C: ATP Yield

5.4D: Respiration and Proton Motive Force

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5.4A: Importance of Glycolysis

Learning Objectives

- Explain the importance of glycolysis to cells

Nearly all of the energy used by living cells comes to them from the energy in the bonds of the sugar glucose. Glucose enters heterotrophic cells in two ways. One method is through secondary active transport in which the transport takes place against the glucose concentration gradient. The other mechanism uses a group of integral proteins called GLUT proteins, also known as glucose transporter proteins. These transporters assist in the facilitated diffusion of glucose. Glycolysis is the first pathway used in the breakdown of glucose to extract energy. It takes place in the cytoplasm of both prokaryotic and eukaryotic cells. It was probably one of the earliest metabolic pathways to evolve since it is used by nearly all of the organisms on earth. The process does not use oxygen and is, therefore, anaerobic.

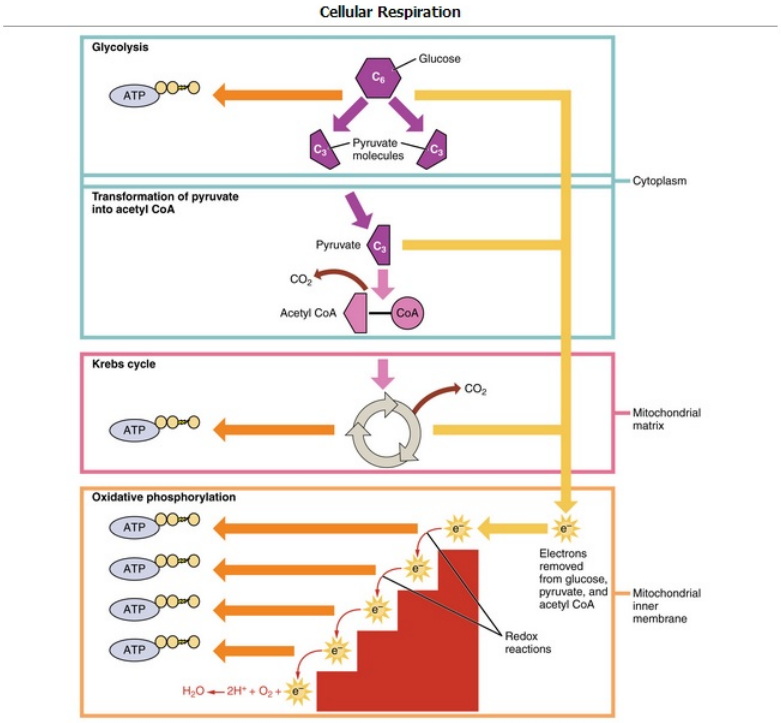

Figure: ***Cellular Respiration****: Glycolysis is the first pathway of cellular respiration that oxidizes glucose molecules. It is followed by the Krebs cycle and oxidative phosphorylation to produce ATP.*

Glycolysis is the first of the main metabolic pathways of cellular respiration to produce energy in the form of ATP. Through two distinct phases, the six-carbon ring of glucose is cleaved into two three-carbon sugars of pyruvate through a series of enzymatic reactions. The first phase of glycolysis requires energy, while the second phase completes the conversion to pyruvate and produces ATP and NADH for the cell to use for energy. Overall, the process of glycolysis produces a net gain of two pyruvate molecules, two ATP molecules, and two NADH molecules for the cell to use for energy. Following the conversion of glucose to pyruvate, the glycolytic pathway is linked to the Krebs Cycle, where further ATP will be produced for the cell's energy needs.

Key Points

- Glycolysis is present in nearly all living organisms.
- Glucose is the source of almost all energy used by cells.
- Overall, glycolysis produces two pyruvate molecules, a net gain of two ATP molecules, and two NADH molecules.

Key Terms

- **glycolysis**: the cellular metabolic pathway of the simple sugar glucose to yield pyruvic acid and ATP as an energy source
- **heterotroph**: an organism that requires an external supply of energy in the form of food, as it cannot synthesize its own

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5.4B: Electron Donors and Acceptors

Learning Objectives

- Recognize the various types of electron donors and acceptors

In prokaryotes (bacteria and archaea) there are several different electron donors and several different electron acceptors. Note that electrons can enter the chain at three levels: at the level of a dehydrogenase, at the level of the quinone pool, or at the level of a mobile cytochrome electron carrier. These levels correspond to successively more positive redox potentials, or to successively decreased potential differences relative to the terminal electron acceptor. In other words, they correspond to successively smaller Gibbs free energy changes for the overall redox reaction *Donor* → *Acceptor*.

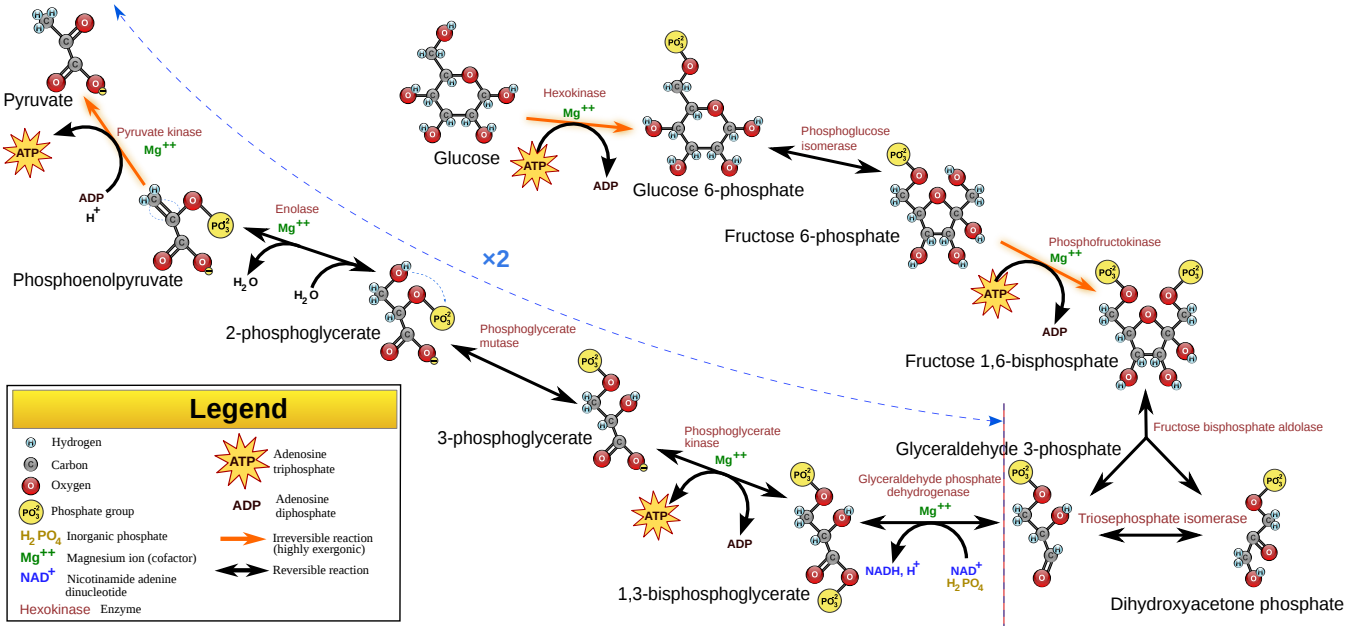

Figure: ***Glycolysis Pathway Overview****: An overview of the glycolytic pathway. This pathway, comprised of a series of reactions, produces many intermediates and molecules utilized as substrates for biosynthesis in additional pathways.*

Individual bacteria use multiple electron transport chains, often simultaneously. Bacteria can use a number of different electron donors, a number of different dehydrogenases, a number of different oxidases and reductases, and a number of different electron acceptors. For example, *E. coli* (when growing aerobically using glucose as an energy source) uses two different NADH dehydrogenases and two different quinol oxidases, for a total of four different electron transport chains operating simultaneously.

A common feature of all electron transport chains is the presence of a proton pump to create a transmembrane proton gradient. Bacterial electron transport chains may contain as many as three proton pumps, like mitochondria, or they may contain only one or two. They always contain at least one proton pump.

In the present day biosphere, the most common electron donors are organic molecules. Organisms that use organic molecules as an energy source are called *organotrophs*. Organotrophs (animals, fungi, protists) and *phototrophs* (plants and algae) constitute the vast majority of all familiar life forms.

Some prokaryotes can use inorganic matter as an energy source. Such organisms are called *lithotrophs* (“rock-eaters”). Inorganic electron donors include hydrogen, carbon monoxide, ammonia, nitrite, sulfur, sulfide, and ferrous iron. Lithotrophs have been found growing in rock formations thousands of meters below the surface of Earth. Because of their volume of distribution, lithotrophs may actually out number organotrophs and phototrophs in our biosphere.

The use of inorganic electron donors as an energy source is of particular interest in the study of evolution. This type of metabolism must logically have preceded the use of organic molecules as an energy source.

Just as there are a number of different electron donors (organic matter in organotrophs, inorganic matter in lithotrophs), there are a number of different electron acceptors, both organic and inorganic. If oxygen is available, it is invariably used as the terminal electron acceptor, because it generates the greatest Gibbs free energy change and produces the most energy.

In anaerobic environments, different electron acceptors are used, including nitrate, nitrite, ferric iron, sulfate, carbon dioxide, and small organic molecules such as fumarate.

Since electron transport chains are redox processes, they can be described as the sum of two redox pairs. For example, the mitochondrial electron transport chain can be described as the sum of the NAD^+/NADH redox pair and the O_2/H_2O redox pair. NADH is the electron donor and O_2 is the electron acceptor.

Not every donor-acceptor combination is thermodynamically possible. The redox potential of the acceptor must be more positive than the redox potential of the donor. Furthermore, actual environmental conditions may be far different from *standard* conditions (1 molar concentrations, 1 atm partial pressures, pH = 7), which apply to *standard* redox potentials. For example, hydrogen-evolving bacteria grow at an ambient partial pressure of hydrogen gas of 10^{-4} atm. The associated redox reaction, which is thermodynamically favorable in nature, is thermodynamically impossible under "standard" conditions.

Bacterial electron transport pathways are, in general, inducible. Depending on their environment, bacteria can synthesize different transmembrane complexes and produce different electron transport chains in their cell membranes. Bacteria select their electron transport chains from a DNA library containing multiple possible dehydrogenases, terminal oxidases and terminal reductases. The situation is often summarized by saying that electron transport chains in bacteria are *branched*, *modular*, and *inducible*.

Key Points

- Bacterial electron transport chains may contain as many as three proton pumps.
- The most common electron donors are organic molecules.
- There are a number of different electron acceptors, both organic and inorganic. If oxygen is available, it is invariably used as the terminal electron acceptor.

Key Terms

- **organotroph**: An organism that obtains its energy from organic compounds.
- **lithotroph**: An organism that obtains its energy from inorganic compounds (such as ammonia) via electron transfer.

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5.4C: ATP Yield

The amount of energy (as ATP) gained from glucose catabolism varies across species and depends on other related cellular processes.

Learning Objectives

- Describe the origins of variability in the amount of ATP that is produced per molecule of glucose consumed

Key Points

- While glucose catabolism always produces energy, the amount of energy (in terms of ATP equivalents) produced can vary, especially across different species.
- The number of hydrogen ions the electron transport chain complexes can pump through the membrane varies between species.
- NAD^+ provides more ATP than FAD^+ in the electron transport chain and can lead to variance in ATP production.
- The use of intermediates from glucose catabolism in other biosynthetic pathways, such as amino acid synthesis, can lower the yield of ATP.

Key Terms

- **catabolism**: Destructive metabolism, usually including the release of energy and breakdown of materials.

ATP Yield

In a eukaryotic cell, the process of cellular respiration can metabolize one molecule of glucose into 30 to 32 ATP. The process of glycolysis only produces two ATP, while all the rest are produced during the electron transport chain. Clearly, the electron transport chain is vastly more efficient, but it can only be carried out in the presence of oxygen.

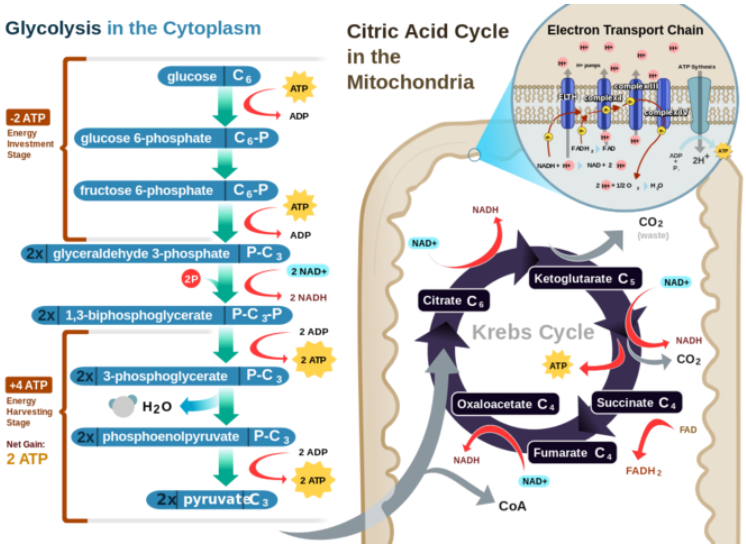

Figure: **Cellular respiration in a eukaryotic cell**: Glycolysis on the left portion of this illustration can be seen to yield 2 ATP molecules, while the Electron Transport Chain portion at the upper right will yield the remaining 30-32 ATP molecules under the presence of oxygen.

The number of ATP molecules generated via the catabolism of glucose can vary substantially. For example, the number of hydrogen ions the electron transport chain complexes can pump through the membrane varies between species. Another source of variance occurs during the shuttle of electrons across the membranes of the mitochondria. The NADH generated from glycolysis cannot easily enter mitochondria. Thus, electrons are picked up on the inside of mitochondria by either NAD^+ or FAD^+. These FAD^+ molecules can transport fewer ions; consequently, fewer ATP molecules are generated when FAD^+ acts as a carrier. NAD^+ is used as the electron transporter in the liver, and FAD^+ acts in the brain.

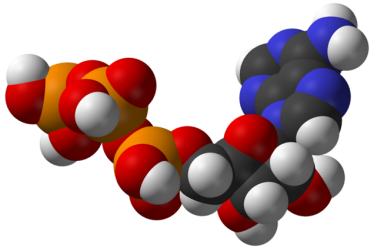

Figure: **Adenosine triphosphate**: ATP is the main source of energy in many living organisms.

Another factor that affects the yield of ATP molecules generated from glucose is the fact that intermediate compounds in these pathways are used for other purposes. Glucose catabolism connects with the pathways that build or break down all other biochemical compounds in cells, but the result is not always ideal. For example, sugars other than glucose are fed into the glycolytic pathway for energy extraction. Moreover, the five-carbon sugars that form nucleic acids are made from intermediates in glycolysis. Certain nonessential amino acids can be made from intermediates of both glycolysis and the citric acid cycle. Lipids, such as cholesterol and triglycerides, are also made from intermediates in these pathways, and both amino acids and triglycerides are broken down for energy through these pathways. Overall, in living systems, these pathways of glucose catabolism extract about 34 percent of the energy contained in glucose.

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5.4D: Respiration and Proton Motive Force

Respiration is one of the key ways a cell gains useful energy to fuel cellular activity.

Learning Objectives

- Describe the role of the proton motive force in respiration

Key Points

- The reactions involved in respiration are catabolic reactions, which break large molecules into smaller ones, releasing energy in the process as they break high-energy bonds.
- Aerobic respiration requires oxygen in order to generate energy (ATP).
- Aerobic metabolism is up to 15 times more efficient than anaerobic metabolism (which yields two molecules ATP per one molecule glucose).
- With the help of the solar-driven enzyme bacteriorhodopsin, some bacteria make proton gradients by pumping in protons from the environment.

Key Terms

- **exothermic**: releasing energy in the form of heat
- **redox**: a reversible process in which one reaction is an oxidation and the reverse is a reduction

Cellular Respiration

Cellular respiration is a set of metabolic reactions and processes that take place within the cells of organisms to convert biochemical energy from nutrients into adenosine triphosphate (ATP). The reactions involved in this respiration are considered to be catabolic reactions that release energy as larger molecules are broken down into smaller ones and high-energy bonds are broken. Respiration is one of the key ways a cell gains useful energy to fuel cellular activity.

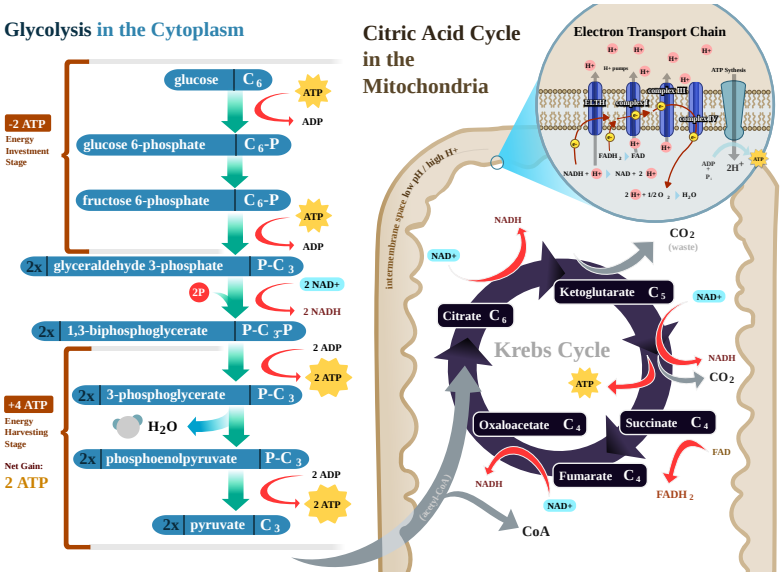

Figure: **Overview of Cellular Respiration**: A diagram of cellular respiration including glycolysis, Krebs cycle (AKA citric acid cycle), and the electron transport chain.

Chemically, cellular respiration is considered an exothermic redox reaction. The overall reaction is broken into many smaller ones when it occurs in the body. Most of these smaller reactions are redox reactions themselves. Although technically, cellular respiration is a combustion reaction, it does not resemble one when it occurs in a living cell. This is because it occurs in many separate steps. While the overall reaction is a combustion reaction, no single reaction that comprises it is a combustion reaction.

Aerobic and Anaerobic Reactions

Aerobic reactions require oxygen for ATP generation. Although carbohydrates, fats and proteins can be used as reactants, the preferred method is the process of glycolysis. During glycolysis, pyruvate is formed from glucose metabolism. During aerobic conditions, the pyruvate enters the mitochondrion to be fully oxidized by the Krebs cycle. The products of the Krebs cycle include energy in the form of ATP (via substrate level phosphorylation), NADH, and FADH2.

The simplified reaction is as follows:

$C_6H_{12}O_6$ (s) + 6 O_2 (g) → 6 CO_2 (g) + 6 H_2O (l) + heat

ΔG = -2880 kJ per mole of $C_6H_{12}O_6$

A negative ΔG indicates that the reaction can occur spontaneously.

Aerobic metabolism is up to 15 times more efficient than anaerobic metabolism, which yields two molecules ATP per one molecule glucose. Both types of metabolism share the initial pathway of glycolysis, but aerobic metabolism continues with the Krebs cycle and oxidative phosphorylation. In eukaryotic cells, the post-glycolytic reactions take place in the mitochondria, while in prokaryotic cells, these reactions take place in the cytoplasm.

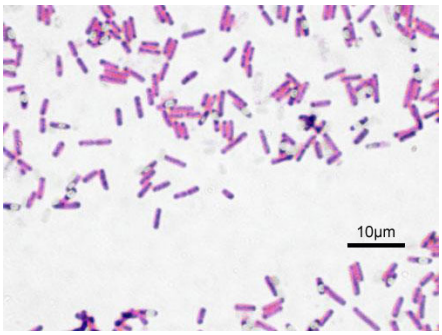

Figure: **Humans use of prokaryotes**: This is a microscopic image of Bacillus subtilis (ATCC 6633) with a gram staining of magnification: 1,000. The oval, unstained structures are spores.

Glycolysis

Glycolysis takes place in the cytosol, does not require oxygen, and can therefore function under anaerobic conditions. The process converts one molecule of glucose into two molecules of pyruvate, generating energy in the form of two net molecules of ATP. Four molecules of ATP per glucose are actually produced, but two of these are consumed as part of the preparatory phase. The initial phosphorylation of glucose is required to destabilize the molecule for cleavage into two pyruvate. During the pay-off phase of glycolysis, four phosphate groups are transferred to ADP by substrate-level phosphorylation to make four ATP, and two NADH are produced when the pyruvate are oxidized. The overall reaction can be expressed this way:

Glucose + 2 NAD^+ + 2 P_i + 2 ADP → 2 pyruvate + 2 NADH + 2 ATP + 2 H^+ + 2 H_2O + heat

Starting with glucose, one ATP is used to donate a phosphate to glucose to produce glucose 6-phosphate. With the help of glycogen phosphorylase, glycogen can change into glucose 6-phosphate as well. During energy metabolism, glucose 6-phosphate turns into fructose 6-phosphate. With the help of phosphofructokinase, an additional ATP can be used to turn phosphorylate fructose 6-phosphate into fructose 1, 6-diphosphate. Fructose 1, 6-diphosphate then splits into two phosphorylated molecules with three carbon chains that later degrades into pyruvate.

Making Proton Gradients

Some archaea, the most notable ones being halobacteria, make proton gradients by pumping in protons from the environment. They are able to do this with the help of the solar-driven enzyme bacteriorhodopsin, which is used to drive the molecular motor enzyme ATP synthase to make the necessary conformational changes required to synthesize ATP. By running ATP synthase in reverse, proton gradients are also made by bacteria and are used to drive flagella. The F1FO ATP synthase is a reversible enzyme. Large enough quantities of ATP cause it to create a transmembrane proton gradient. This is used by fermenting bacteria, which lack an electron transport chain, and which hydrolyze ATP to make a proton gradient. Bacteria use these gradients for flagella and for the transportation of nutrients into the cell. In respiring bacteria under physiological conditions, ATP synthase, in general, runs in the

opposite direction. This creates ATP while using the proton motive force created by the electron transport chain as a source of energy. The overall process of creating energy in this fashion is termed oxidative phosphorylation.

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SECTION OVERVIEW

5.5: Respiratory ETS and ATP Synthase

Topic hierarchy

5.5A: Cofactors and Energy Transitions

5.5B: Oxidoreductase Protein Complexes

5.5C: F10 ATP Synthase

5.5D: Sodium Pumps as an Alternative to Proton Pump

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5.5A: Cofactors and Energy Transitions

A cofactor is a non-protein chemical compound that is bound to a protein and is required for the protein's biological activity.

Learning Objectives

- Recognize the various types of cofactors involved in biochemical reactions

Key Points

- Cofactors are commonly enzymes, and cofactors can be considered "helper molecules " that assist in biochemical transformations.
- Some enzymes or enzyme complexes require several cofactors.
- Each class of group-transfer reaction is carried out by a particular cofactor, which is the substrate for a set of enzymes that produce it, and a set of enzymes that consume it.

Key Terms

- **cofactor**: A substance, especially a coenzyme or a metal, that must be present for an enzyme to function.
- **enzymes**: Enzymes are large biological molecules responsible for the thousands of chemical interconversions that sustain life. They are highly selective catalysts, greatly accelerating both the rate and specificity of metabolic reactions, from the digestion of food to the synthesis of DNA.
- **reaction**: A chemical reaction is a process that leads to the transformation of one set of chemical substances to another. Classically, chemical reactions encompass changes that strictly involve the motion of electrons in the forming and breaking of chemical bonds between atoms, and can often be described by a chemical equation.
- **apoenzyme**: an inactive haloenzyme lacking a cofactor

A cofactor is a non- protein chemical compound that is bound to a protein and is required for the protein's biological activity. These proteins are commonly enzymes. Cofactors can be considered "helper molecules" that assist in biochemical transformations.

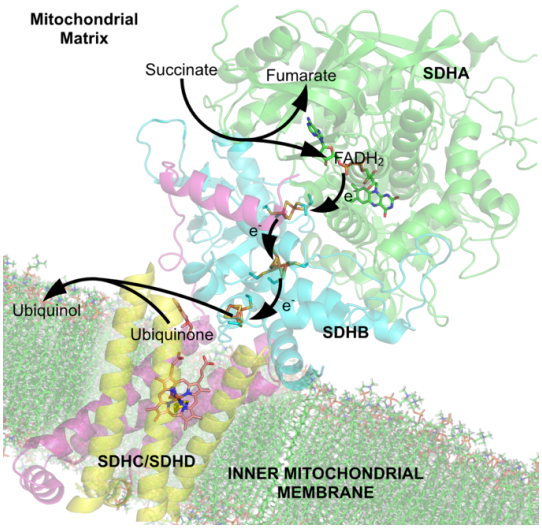

Figure: **Cofactor**: The succinate dehydrogenase complex showing several cofactors, including flavin, iron-sulfur centers, and heme.

Cofactors are either organic or inorganic. They can also be classified depending on how tightly they bind to an enzyme, with loosely-bound cofactors termed coenzymes and tightly-bound cofactors termed prosthetic groups. Some sources also limit the use of the term "cofactor" to inorganic substances. An inactive enzyme without the cofactor is called an apoenzyme, while the complete enzyme with cofactor is the holoenzyme.

Some enzymes or enzyme complexes require several cofactors. For example, the multienzyme complex pyruvate dehydrogenase at the junction of glycolysis and the citric acid cycle requires five organic cofactors and one metal ion: loosely bound thiamine pyrophosphate (TPP), covalently bound lipoamide and flavin adenine dinucleotide (FAD), and the cosubstrates nicotinamide adenine dinucleotide (NAD+) and coenzyme A (CoA), and a metal ion (Mg^{2+}).

Organic cofactors are often vitamins or are made from vitamins. Many contain the nucleotide adenosine monophosphate (AMP) as part of their structures, such as ATP, coenzyme A, FAD, and NAD+. This common structure may reflect a common evolutionary origin as part of ribozymes in an ancient RNA world. It has been suggested that the AMP part of the molecule can be considered a kind of “handle” by which the enzyme can “grasp” the coenzyme to switch it between different catalytic centers.

Cofactors can be divided into two broad groups: organic cofactors, such as flavin or heme, and inorganic cofactors, such as the metal ions Mg2+, Cu+, Mn2+, or iron-sulfur clusters.

Vitamins can serve as precursors to many organic cofactors (e.g., vitamins B1, B2, B6, B12, niacin, folic acid) or as coenzymes themselves (e.g., vitamin C). However, vitamins do have other functions in the body. Many organic cofactors also contain a nucleotide, such as the electron carriers NAD and FAD, and coenzyme A, which carries acyl groups. Most of these cofactors are found in a huge variety of species, and some are universal to all forms of life. An exception to this wide distribution is a group of unique cofactors that evolved in methanogens, which are restricted to this group of archaea.

Metabolism involves a vast array of chemical reactions, but most fall under a few basic types of reactions that involve the transfer of functional groups. This common chemistry allows cells to use a small set of metabolic intermediates to carry chemical groups between different reactions. These group-transfer intermediates are the loosely-bound organic cofactors, often called coenzymes.

Each class of group-transfer reaction is carried out by a particular cofactor, which is the substrate for a set of enzymes that produce it and a set of enzymes that consume it. An example of this is the dehydrogenases that use nicotinamide adenine dinucleotide (NAD+) as a cofactor. Here, hundreds of separate types of enzymes remove electrons from their substrates and reduce NAD+ to NADH. This reduced cofactor is then a substrate for any of the reductases in the cell that require electrons to reduce their substrates.

Therefore, these cofactors are continuously recycled as part of metabolism. As an example, the total quantity of ATP in the human body is about 0.1 mole. This ATP is constantly being broken down into ADP, and then converted back into ATP. Therefore, at any given time, the total amount of ATP + ADP remains fairly constant. The energy used by human cells requires the hydrolysis of 100 to 150 moles of ATP daily, which is around 50 to 75 kg. In typical situations, humans use up their body weight of ATP over the course of the day. This means that each ATP molecule is recycled 1,000 to 1,500 times daily.

The term is used in other areas of biology to refer more broadly to non-protein (or even protein) molecules that either activate, inhibit, or are required for the protein to function. For example, ligands such as hormones that bind to and activate receptor proteins are termed cofactors or coactivators, whereas molecules that inhibit receptor proteins are termed corepressors.

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5.5B: Oxidoreductase Protein Complexes

In biochemistry, an oxidoreductase is an enzyme that catalyzes the transfer of electrons from one molecule to another.

Learning Objectives

- Recognize the function of oxidoreductase protein complexes

Key Points

- The reductant is the electron donor.
- The oxidant is the electron acceptor.
- This group of enzymes usually utilizes NADP or NAD+ as cofactors.

Key Terms

- **oxidoreductase**: Any enzyme that catalyzes an oxidation-reduction (redox) reaction.
- **enzyme**: A globular protein that catalyses a biological chemical reaction.
- **catalyzes**: Catalysis is the change in rate of a chemical reaction due to the participation of a substance called a catalyst. Unlike other reagents that participate in the chemical reaction, a catalyst is not consumed by the reaction itself.

In biochemistry, an oxidoreductase is an enzyme that catalyzes the transfer of electrons from one molecule, the reductant, also called the electron donor, to another the oxidant, also called the electron acceptor. This group of enzymes usually utilizes NADP or NAD+ as cofactors.

For example, an enzyme that catalyzed this reaction would be an oxidoreductase: A– + B → A + B–. In this example, A is the reductant (electron donor) and B is the oxidant (electron acceptor).

In biochemical reactions, the redox reactions are sometimes more difficult to see, such as this reaction from glycolysis: Pi + glyceraldehyde-3-phosphate + NAD+ → NADH + H+ + 1,3-bisphosphoglycerate. In this reaction, NAD+ is the oxidant (electron acceptor) and glyceraldehyde-3-phosphate is the reductant (electron donor).

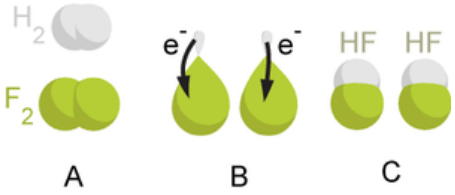

Figure: **Illustration of a redox reaction**: Illustration of a redox reaction

Oxidoreductases are classified as EC 1 in the EC number classification of enzymes. Oxidoreductases can be further classified into 22 subclasses:

- EC 1.1 includes oxidoreductases that act on the CH-OH group of donors (alcohol oxidoreductases);
- EC 1.2 includes oxidoreductases that act on the aldehyde or oxo group of donors;
- EC 1.3 includes oxidoreductases that act on the CH-CH group of donors (CH-CH oxidoreductases);
- EC 1.4 includes oxidoreductases that act on the CH-NH_2 group of donors (Amino acid oxidoreductases, Monoamine oxidase);
- EC 1.5 includes oxidoreductases that act on CH-NH group of donors;
- EC 1.6 includes oxidoreductases that act on NADH or NADPH;
- EC 1.7 includes oxidoreductases that act on other nitrogenous compounds as donors;
- EC 1.8 includes oxidoreductases that act on a sulfur group of donors;
- EC 1.9 includes oxidoreductases that act on a heme group of donors;
- EC 1.10 includes oxidoreductases that act on diphenols and related substances as donors;
- EC 1.11 includes oxidoreductases that act on peroxide as an acceptor (peroxidases);
- EC 1.12 includes oxidoreductases that act on hydrogen as donors;
- EC 1.13 includes oxidoreductases that act on single donors with incorporation of molecular oxygen (oxygenases);
- EC 1.14 includes oxidoreductases that act on paired donors with incorporation of molecular oxygen;
- EC 1.15 includes oxidoreductases that act on superoxide radicals as acceptors;
- EC 1.16 includes oxidoreductases that oxidize metal ions; EC 1.17 includes oxidoreductases that act on CH or CH2 groups;

- EC 1.18 includes oxidoreductases that act on iron-sulfur proteins as donors;
- EC 1.19 includes oxidoreductases that act on reduced flavodoxin as a donor;
- EC 1.20 includes oxidoreductases that act on phosphorus or arsenic in donors;
- EC 1.21 includes oxidoreductases that act on X-H and Y-H to form an X-Y bond; and EC 1.97 includes other oxidoreductases.

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5.5C: F10 ATP Synthase

ATP synthase is an important enzyme that provides energy for the cell to use through the synthesis of adenosine triphosphate.

Learning Objectives

- Discuss the structure and function of ATP synthase, including the F1 and FO components

Key Points

- Energy is often released in the form of protium or H+, moving down an electrochemical gradient.
- ATP synthase consists of 2 regions: the FO portion is within the membrane and the F1 portion of the ATP synthase is above the membrane, inside the matrix of the mitochondria.
- E. coli ATP synthase is the simplest known form of ATP synthase, with 8 different subunit types.

Key Terms

- **synthase**: Any enzyme that catalyzes the synthesis of a biological compound but, unlike synthetases, does not make use of ATP as a source of energy
- **adenosine triphosphate**: Adenosine-5′-triphosphate (ATP) is a multifunctional nucleoside triphosphate used in cells as a coenzyme. It is often called the “molecular unit of currency” of intracellular energy transfer.
- **enzyme**: A globular protein that catalyses a biological chemical reaction.

ATP synthase is an important enzyme that provides energy for the cell to use through the synthesis of adenosine triphosphate (ATP). ATP is the most commonly used “energy currency” of cells from most organisms. It is formed from adenosine diphosphate (ADP) and inorganic phosphate (Pi), and needs energy.

The overall reaction sequence is: ATP synthase + ADP + Pi → ATP Synthase + ATP

Energy is often released in the form of protium or H+, moving down an electrochemical gradient, such as from the lumen into the stroma of chloroplasts or from the inter-membrane space into the matrix in mitochondria.

Located within the mitochondria, ATP synthase consists of 2 regions: the FO portion is within the membrane and the F1 portion of the ATP synthase is above the membrane, inside the matrix of the mitochondria.

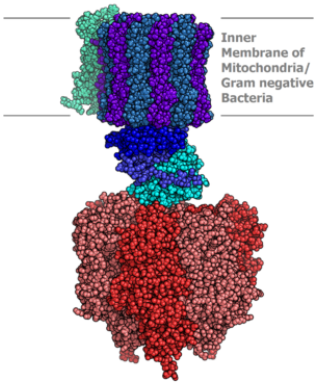

Figure: **ATP synthase**: Molecular model of ATP synthase by X-ray diffraction method

The nomenclature of the enzyme suffers from a long history. The F1 fraction derives its name from the term “Fraction 1” and FO (written as a subscript letter “o”, not “zero”) derives its name from being the oligomycin binding fraction. Oligomycin, an antibiotic, is able to inhibit the FO unit of ATP synthase.

F1- ATP Synthase structure: The F1 particle is large and can be seen in the transmission electron microscope by negative staining. These are particles of 9 nm diameter that pepper the inner mitochondrial membrane. They were originally called elementary particles and were thought to contain the entire respiratory apparatus of the mitochondrion, but, through a long series of experiments, Ephraim Racker and his colleagues (who first isolated the F1 particle in 1961) were able to show that this particle is correlated with ATPase activity in uncoupled mitochondria and with the ATPase activity in submitochondrial particles created by

exposing mitochondria to ultrasound. This ATPase activity was further associated with the creation of ATP by a long series of experiments in many laboratories.

The FO region of ATP synthase is a proton pore that is embedded in the mitochondrial membrane. It consists of three main subunits A, B, and C, and (in humans) six additional subunits, d, e, f, g, F6, and 8 (or A6L).

E. coli ATP synthase is the simplest known form of ATP synthase, with 8 different subunit types.

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5.5D: Sodium Pumps as an Alternative to Proton Pump

Most bacteria rely on proton motive force as a source of energy for a variety of cellular processes.

Learning Objectives

- Describe the mechanisms of sodium pumps and its role as an alternative proton pump

Key Points

- The Na+/K+-ATPase helps maintain resting potential, avail transport and regulate cellular volume.
- The pump, while binding ATP, binds 3 intracellular Na+ ions. ATP is hydrolyzed, leading to phosphorylation of the pump at a highly conserved aspartate residue and subsequent release of ADP.
- Some extremophilic bacteria can use Na+ as a coupling ion in an Na+ cycle instead of, or in addition to, the H+ cycle.
- Na+-based membrane energetics provide an additional means of ATP synthesis, motility and solute uptake for pathogenic microbes.
- Because Na+ concentrations in most natural environments are almost 10^6-fold higher than H+ concentrations, sodium motive force levels are unlikely to change as rapidly as proton motive force levels, making sodium motive force a much more reliable source of energy.

Key Terms

- **antiporter**: A cell protein that acts within an antiport to transport different molecules or ions across the membrane in opposite directions
- **resting potential**: The nearly latent membrane potential of inactive cells.
- **hydrolyzed**: Hydrolysis usually means the cleavage of chemical bonds by the addition of water.

What Are Sodium Pumps?

Na+/K+-ATPase (Sodium-potassium adenosine triphosphatase, also known as Na+/K+ pump, sodium-potassium pump, or sodium pump) is an antiporter enzyme (EC 3.6.3.9) (an electrogenic transmembrane ATPase) located in the plasma membrane of all animal cells.

Active transport is responsible for cells containing relatively high concentrations of potassium ions but low concentrations of sodium ions. The mechanism responsible for this is the sodium-potassium pump, which moves these two ions in opposite directions across the plasma membrane. This was investigated by following the passage of radioactively labeled ions across the plasma membrane of certain cells. It was found that the concentrations of sodium and potassium ions on the two sides of the membrane are interdependent, suggesting that the same carrier transports both ions. It is now known that the carrier is an ATP-ase and that it pumps three sodium ions out of the cell for every two potassium ions pumped in.

Discovery and Significance

The sodium-potassium pump was discovered in the 1950s by Danish scientist Jens Christian Skou. It marked an important step in our understanding of how ions get into and out of cells, and has a particular significance for excitable cells like nervous cells, which depend on this pump for responding to stimuli and transmitting impulses.

The Na+/K+-ATPase helps maintain resting potential, avail transport and regulate cellular volume. It also functions as signal transducer/integrator to regulate MAPK pathway, ROS, as well as intracellular calcium. In most animal cells, the Na+/K+-ATPase is responsible for about 1/5 of the cell's energy expenditure. For neurons, the Na+/K+-ATPase can be responsible for up to 2/3 of the cell's energy expenditure.

Functions

Functions include resting potential, transport, controlling cell volume and acting as a signal transducer. The pump, while binding ATP, binds 3 intracellular Na+ ions. ATP is hydrolyzed, leading to phosphorylation of the pump at a highly conserved aspartate residue and subsequent release of ADP. A conformational change in the pump exposes the Na+ ions to the outside. The phosphorylated form of the pump has a low affinity for Na+ ions, so they are released.The pump binds 2 extracellular K+ ions. This causes the dephosphorylation of the pump, reverting it to its previous conformational state, transporting the K+ ions into the

cell.The unphosphorylated form of the pump has a higher affinity for Na+ ions than K+ ions, so the two bound K+ ions are released. ATP binds, and the process starts again.

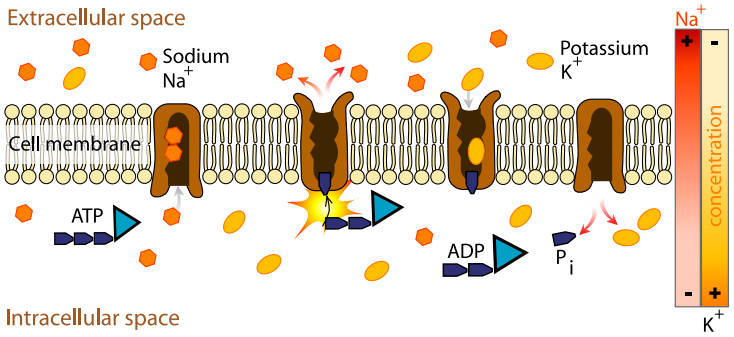

Figure: **Na+/K+-ATPase**: Na+/K+-ATPase Mechanism of Action

Proton Motive Force

Most bacteria rely on proton motive force as a source of energy for a variety of cellular processes. Usually, an H+ cycle includes generation of the transmembrane electrochemical gradient of H+ (proton motive force) by primary transport systems (H+ pumps) and its use for ATP synthesis, solute transport, motility and reverse electron transport. A substantial body of evidence indicates, however, that certain extremophilic bacteria can use Na+ as a coupling ion in an Na+ cycle instead of, or in addition to, the H+ cycle. As in the H+ cycle, a fully operational Na+ cycle would include a primary Na+ pump that directly couples Na+ translocation to a chemical reaction, an Na+-transporting membrane ATP synthetase, a number of Na+-dependent membrane transporters, and an Na+-dependent flagellar motor. While certain Na+-dependent functions, like Na+-dependent uptake of melibiose, proline, and glutamate, have been observed in many bacteria, the ion gradients that served as energy sources for these transports have been generated by primary H+ pumps and converted to Na+ gradients by Na+/H+ antiporters.

One could think of several possible explanations for the widespread distribution of the elements of the Na+ cycle among pathogenic bacteria. First, Na+-based membrane energetics could improve the versatility of a pathogen by providing it with additional means of ATP synthesis, motility and solute uptake. This would improve its chances for colonization of the host cells and survival in the host organisms where defense mechanisms, including generation of superoxide radicals, impair the integrity of the bacterial membrane and decrease the levels of the proton motive force. Second, because Na+ concentrations in most natural environments are almost 10^6-fold higher than H+ concentrations, sodium motive force levels are unlikely to change as rapidly as proton motive force levels, making sodium motive force a much more reliable source of energy.

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SECTION OVERVIEW

5.6: The Citric Acid (Krebs) Cycle

Topic hierarchy

5.6A: Citric Acid Cycle

5.6B: Breakdown of Pyruvate

5.6C: Acetyl CoA and the Citric Acid Cycle

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5.6A: Citric Acid Cycle

Learning Objectives

- List the steps of the Krebs (or citric acid) cycle

Like the conversion of pyruvate to acetyl CoA, the citric acid cycle takes place in the matrix of the mitochondria. Almost all of the enzymes of the citric acid cycle are soluble, with the single exception of the enzyme succinate dehydrogenase, which is embedded in the inner membrane of the mitochondrion. Unlike glycolysis, the citric acid cycle is a closed loop: the last part of the pathway regenerates the compound used in the first step. The eight steps of the cycle are a series of redox, dehydration, hydration, and decarboxylation reactions that produce two carbon dioxide molecules, one GTP/ATP, and reduced forms of NADH and FADH2. This is considered an aerobic pathway because the NADH and FADH2 produced must transfer their electrons to the next pathway in the system, which will use oxygen. If this transfer does not occur, the oxidation steps of the citric acid cycle also do not occur. Note that the citric acid cycle produces very little ATP directly and does not directly consume oxygen.

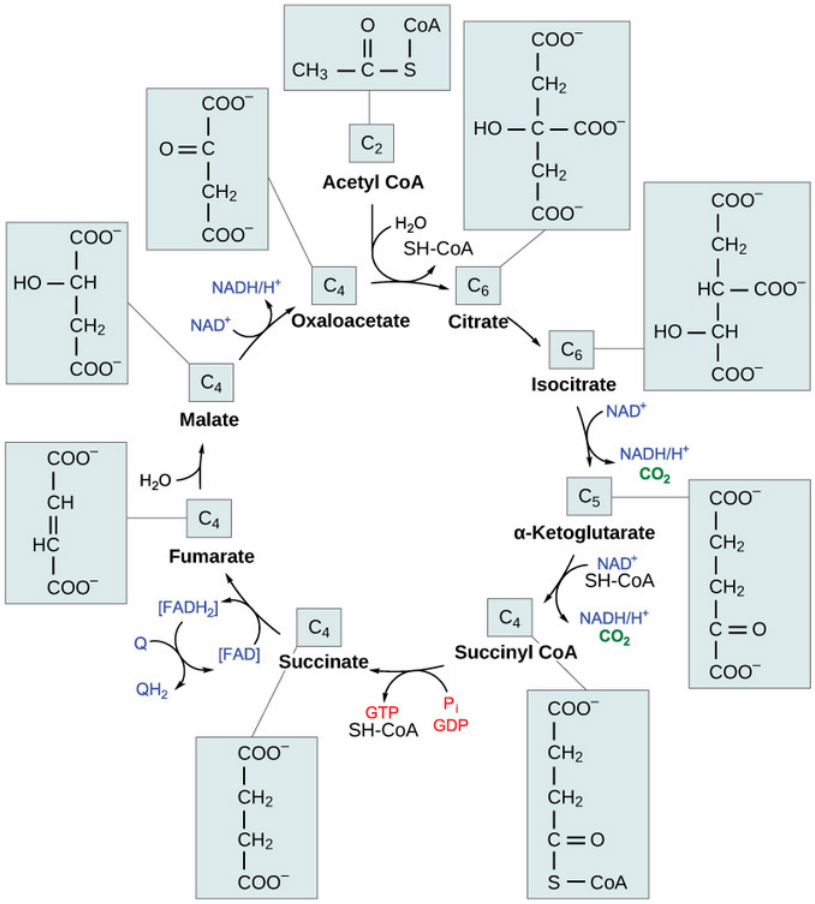

Figure: ***The citric acid cycle****: In the citric acid cycle, the acetyl group from acetyl CoA is attached to a four-carbon oxaloacetate molecule to form a six-carbon citrate molecule. Through a series of steps, citrate is oxidized, releasing two carbon dioxide molecules for each acetyl group fed into the cycle. In the process, three NAD+ molecules are reduced to NADH, one FAD molecule is reduced to $FADH_2$, and one ATP or GTP (depending on the cell type) is produced (by substrate-level phosphorylation). Because the final product of the citric acid cycle is also the first reactant, the cycle runs continuously in the presence of sufficient reactants.*

Steps in the Citric Acid Cycle

Step 1. The first step is a condensation step, combining the two-carbon acetyl group (from acetyl CoA) with a four-carbon oxaloacetate molecule to form a six-carbon molecule of citrate. CoA is bound to a sulfhydryl group (-SH) and diffuses away to eventually combine with another acetyl group. This step is irreversible because it is highly exergonic. The rate of this reaction is controlled by negative feedback and the amount of ATP available. If ATP levels increase, the rate of this reaction decreases. If ATP is in short supply, the rate increases.

Step 2. Citrate loses one water molecule and gains another as citrate is converted into its isomer, isocitrate.

Steps 3 and 4. In step three, isocitrate is oxidized, producing a five-carbon molecule, α-ketoglutarate, together with a molecule of CO_2 and two electrons, which reduce NAD+ to NADH. This step is also regulated by negative feedback from ATP and NADH and by a positive effect of ADP. Steps three and four are both oxidation and decarboxylation steps, which release electrons that reduce NAD^+ to NADH and release carboxyl groups that form CO_2 molecules. α-Ketoglutarate is the product of step three, and a succinyl group is the product of step four. CoA binds the succinyl group to form succinyl CoA. The enzyme that catalyzes step four is regulated by feedback inhibition of ATP, succinyl CoA, and NADH.

Step 5. A phosphate group is substituted for coenzyme A, and a high- energy bond is formed. This energy is used in substrate-level phosphorylation (during the conversion of the succinyl group to succinate) to form either guanine triphosphate (GTP) or ATP. There are two forms of the enzyme, called isoenzymes, for this step, depending upon the type of animal tissue in which they are found. One form is found in tissues that use large amounts of ATP, such as heart and skeletal muscle. This form produces ATP. The second form of the enzyme is found in tissues that have a high number of anabolic pathways, such as liver. This form produces GTP. GTP is energetically equivalent to ATP; however, its use is more restricted. In particular, protein synthesis primarily uses GTP.

Step 6. Step six is a dehydration process that converts succinate into fumarate. Two hydrogen atoms are transferred to FAD, producing $FADH_2$. The energy contained in the electrons of these atoms is insufficient to reduce NAD^+ but adequate to reduce FAD. Unlike NADH, this carrier remains attached to the enzyme and transfers the electrons to the electron transport chain directly. This process is made possible by the localization of the enzyme catalyzing this step inside the inner membrane of the mitochondrion.

Step 7. Water is added to fumarate during step seven, and malate is produced. The last step in the citric acid cycle regenerates oxaloacetate by oxidizing malate. Another molecule of NADH is produced.

Products of the Citric Acid Cycle

Two carbon atoms come into the citric acid cycle from each acetyl group, representing four out of the six carbons of one glucose molecule. Two carbon dioxide molecules are released on each turn of the cycle; however, these do not necessarily contain the most recently-added carbon atoms. The two acetyl carbon atoms will eventually be released on later turns of the cycle; thus, all six carbon atoms from the original glucose molecule are eventually incorporated into carbon dioxide. Each turn of the cycle forms three NADH molecules and one $FADH_2$ molecule. These carriers will connect with the last portion of aerobic respiration to produce ATP molecules. One GTP or ATP is also made in each cycle. Several of the intermediate compounds in the citric acid cycle can be used in synthesizing non-essential amino acids; therefore, the cycle is amphibolic (both catabolic and anabolic).

Key Points

- The four-carbon molecule, oxaloacetate, that began the cycle is regenerated after the eight steps of the citric acid cycle.
- The eight steps of the citric acid cycle are a series of redox, dehydration, hydration, and decarboxylation reactions.
- Each turn of the cycle forms one GTP or ATP as well as three NADH molecules and one FADH2 molecule, which will be used in further steps of cellular respiration to produce ATP for the cell.

Key Terms

- **citric acid cycle**: a series of chemical reactions used by all aerobic organisms to generate energy through the oxidization of acetate derived from carbohydrates, fats, and proteins into carbon dioxide
- **Krebs cycle**: a series of enzymatic reactions that occurs in all aerobic organisms; it involves the oxidative metabolism of acetyl units and serves as the main source of cellular energy
- **mitochondria**: in cell biology, a mitochondrion (plural mitochondria) is a membrane-enclosed organelle, often described as “cellular power plants” because they generate most of the ATP

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5.6B: Breakdown of Pyruvate

Learning Objectives

- Explain why cells break down pyruvate

In order for pyruvate, the product of glycolysis, to enter the next pathway, it must undergo several changes to become acetyl Coenzyme A (acetyl CoA). Acetyl CoA is a molecule that is further converted to oxaloacetate, which enters the citric acid cycle (Krebs cycle). The conversion of pyruvate to acetyl CoA is a three-step process.

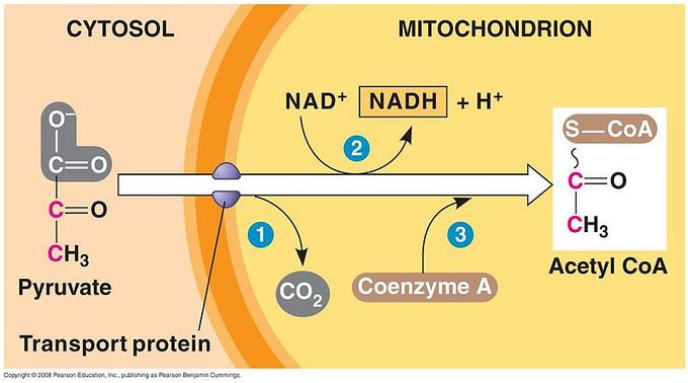

Figure: **Breakdown of Pyruvate**: Each pyruvate molecule loses a carboxylic group in the form of carbon dioxide. The remaining two carbons are then transferred to the enzyme CoA to produce Acetyl CoA.

Step 1. A carboxyl group is removed from pyruvate, releasing a molecule of carbon dioxide into the surrounding medium. (Note: carbon dioxide is one carbon attached to two oxygen atoms and is one of the major end products of cellular respiration.) The result of this step is a two-carbon hydroxyethyl group bound to the enzyme pyruvate dehydrogenase; the lost carbon dioxide is the first of the six carbons from the original glucose molecule to be removed. This step proceeds twice for every molecule of glucose metabolized (remember: there are two pyruvate molecules produced at the end of glycolysis); thus, two of the six carbons will have been removed at the end of both of these steps.

Step 2. The hydroxyethyl group is oxidized to an acetyl group, and the electrons are picked up by NAD^+, forming NADH (the reduced form of NAD+). The high- energy electrons from NADH will be used later by the cell to generate ATP for energy.

Step 3. The enzyme-bound acetyl group is transferred to CoA, producing a molecule of acetyl CoA. This molecule of acetyl CoA is then further converted to be used in the next pathway of metabolism, the citric acid cycle.

Key Points

- In the conversion of pyruvate to acetyl CoA, each pyruvate molecule loses one carbon atom with the release of carbon dioxide.
- During the breakdown of pyruvate, electrons are transferred to NAD+ to produce NADH, which will be used by the cell to produce ATP.
- In the final step of the breakdown of pyruvate, an acetyl group is transferred to Coenzyme A to produce acetyl CoA.

Key Terms

- **acetyl CoA**: a molecule that conveys the carbon atoms from glycolysis (pyruvate) to the citric acid cycle to be oxidized for energy production

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5.6C: Acetyl CoA and the Citric Acid Cycle

Learning Objectives

- Recall the citric acid cycle

The citric acid cycle, shown in —also known as the tricarboxylic acid cycle (TCA cycle) or the Krebs cycle—is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation of acetate—derived from carbohydrates, fats, and proteins—into carbon dioxide. The cycle provides precursors including certain amino acids as well as the reducing agent NADH that is used in numerous biochemical reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest established components of cellular metabolism; it may have originated abiogenically.

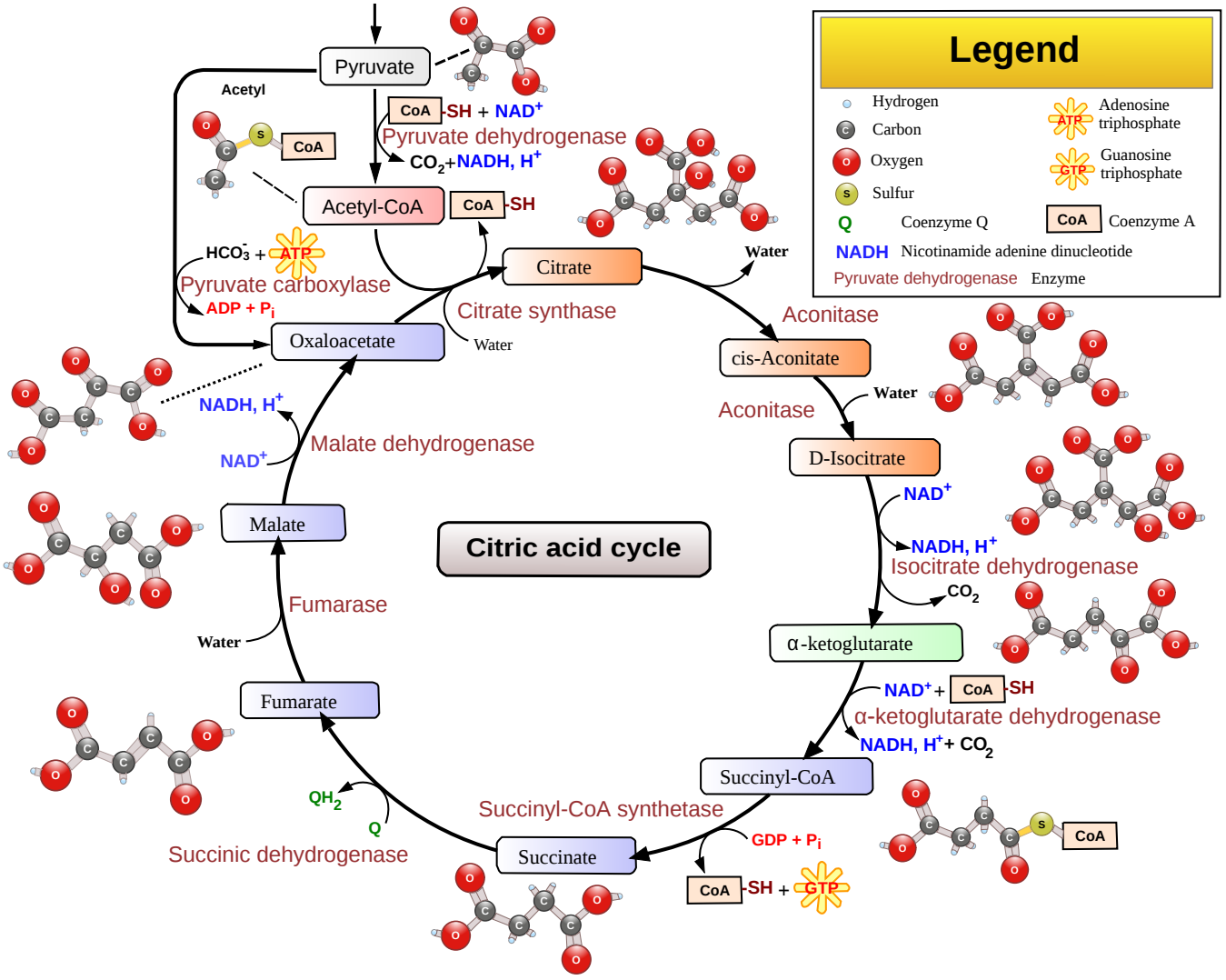

Figure: **The Citric Acid Cycle**: The citric acid cycle, or Krebs cycle, is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidization of acetate—derived from carbohydrates, fats, and proteins—into carbon dioxide. In addition, the cycle provides precursors including certain amino acids as well as the reducing agent NADH that is used in numerous biochemical reactions.

The name of this metabolic pathway is derived from citric acid, a type of tricarboxylic acid that is first consumed and then regenerated by this sequence of reactions to complete the cycle. The cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD^+ to NADH, and produces carbon dioxide. The NADH generated by the TCA cycle is fed into the oxidative phosphorylation pathway. The net result of these two closely linked pathways is the oxidation of nutrients to produce usable energy in the form of ATP.

Components of the TCA cycle were derived from anaerobic bacteria, and the TCA cycle itself may have evolved more than once. Theoretically there are several alternatives to the TCA cycle, however the TCA cycle appears to be the most efficient. If several alternatives independently evolved, they all rapidly converged to the TCA cycle.

The citric acid cycle is a key component of the metabolic pathway by which all aerobic organisms generate energy. Through the catabolism of sugars, fats, and proteins, a two carbon organic product acetate in the form of acetyl-CoA is produced. Acetyl-CoA along with two equivalents of water (H_2O) are consumed by the citric acid cycle, producing two equivalents of carbon dioxide (CO_2) and one equivalent of HS-CoA. In addition, one complete turn of the cycle converts three equivalents of nicotinamide adenine dinucleotide (NAD^+) into three equivalents of reduced NAD^+ (NADH), one equivalent of ubiquinone (Q) into one equivalent of reduced ubiquinone (QH_2), and one equivalent each of guanosine diphosphate (GDP) and inorganic phosphate (P_i) into one equivalent of guanosine triphosphate (GTP). The NADH and QH_2 that is generated by the citric acid cycle is used by the oxidative phosphorylation pathway to generate energy-rich adenosine triphosphate (ATP).

One of the primary sources of acetyl-CoA is sugars that are broken down by glycolysis to produce pyruvate that, in turn, is decarboxylated by the enzyme pyruvate dehydrogenase. This generates acetyl-CoA according to the following reaction scheme:

$CH_3C(=O)C(=O)O^-$ (pyruvate) + HSCoA + NAD^+ → CH3C(=O)SCoA (acetyl-CoA) + NADH + H^+ + CO_2

The product of this reaction, acetyl-CoA, is the starting point for the citric acid cycle.

Key Points

- The Krebs cycle is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidization of acetate—derived from carbohydrates, fats, and proteins —into carbon dioxide.
- Theoretically there are several alternatives to the TCA cycle, but the TCA cycle appears to be the most efficient.
- The citric acid cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD+ to NADH, and produces carbon dioxide.

Key Terms

- **acetyl CoA**: Acetyl coenzyme A or acetyl-CoA is an important molecule in metabolism, used in many biochemical reactions. Its main function is to convey the carbon atoms within the acetyl group to the citric acid cycle (Krebs cycle) to be oxidized for energy production.
- **citric acid cycle**: An alternative name for the Krebs cycle.
- **glycolysis**: The cellular degradation of the simple sugar glucose to yield pyruvic acid and ATP as an energy source.

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SECTION OVERVIEW

5.7: Alternatives to Glycolysis

Topic hierarchy

5.7A: The Entner-Doudoroff Pathway

5.7B: Aerobic Hydrocarbon Oxidation

5.7C: The Pentose Phosphate Shunt

5.7D: Organic Acid Metabolism

5.7E: Lipid Metabolism

5.7F: Connecting Proteins to Glucose Metabolism

5.7G: Methylotrophy and Methanotrophy

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5.7A: The Entner-Doudoroff Pathway

Learning Objectives

- Distinguish between the Entner-Doudoroff pathway and glycolysis

The Entner–Doudoroff pathway describes an alternate series of reactions that catabolize glucose to pyruvate using a set of enzymes different from those used in either glycolysis or the pentose phosphate pathway. Glycolysis (from glycose, an older term for glucose + -lysis degradation) is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate, CH_3COCOO^-. The free energy released in this process is used to form the high-energy compounds ATP (adenosine triphosphate) and NADH (reduced nicotinamide adenine dinucleotide). Most bacteria use glycolysis and the pentose phosphate pathway. This pathway was first reported in 1952 by Michael Doudoroff and Nathan Entner.

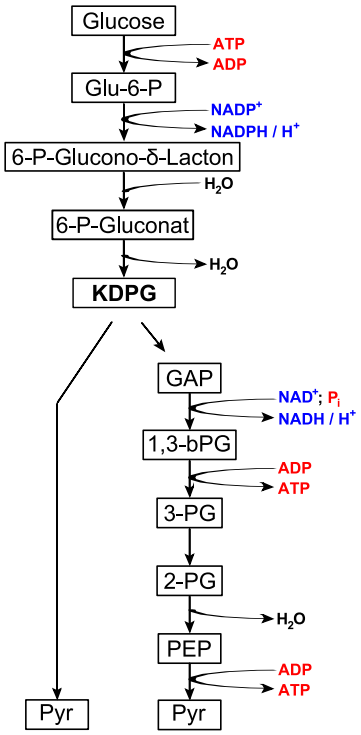

Figure: ***The Entner–Doudoroff Pathway****: This is a diagram of the Entner-Doudoroff pathway (KDPG: 2-keto-3-deoxy-6-phosphogluconate).*

Distinct features of the Entner–Doudoroff pathway are that it occurs only in prokaryotes and it uses 6-phosphogluconate dehydratase and 2-keto-3-deoxyphosphogluconate aldolase to create pyruvate from glucose. The Entner–Doudoroff pathway has a net yield of 1 ATP for every glucose molecule processed, as well as 1 NADH and 1 NADPH. By comparison, glycolysis has a net yield of 2 ATP and 2 NADH for every one glucose molecule processed.

There are a few bacteria that substitute classic glycolysis with the Entner-Doudoroff pathway. They may lack enzymes essential for glycolysis, such as phosphofructokinase-1. This pathway is generally found in *Pseudomonas*, *Rhizobium*, *Azotobacter*, *Agrobacterium*, and a few other Gram-negative genera. Very few Gram-positive bacteria have this pathway, with *Enterococcus faecalis* being a rare exception. Most organisms that use the pathway are aerobes due to the low ATP yield per glucose such as Pseudomonas, a genus of Gram-negative bacteria, and Azotobacter, a genus of Gram-negative bacteria.

Key Points

- Glycolysis is the metabolic pathway that converts glucose into pyruvate and hydrogen ions.
- The Entner-Doudoroff pathway was first reported in 1952 by Michael Doudoroff and Nathan Entner.
- There are a few bacteria that substitute classic glycolysis with the Entner-Doudoroff pathway.

Key Terms

- **glycolysis**: The metabolic pathway that converts glucose into pyruvate and hydrogen ions.
- **ATP**: Adenosine-5′-triphosphate (ATP) is a multifunctional nucleoside triphosphate used in cells as a coenzyme. It is often called the “molecular unit of currency” of intracellular energy transfer. ATP transports chemical energy within cells for metabolism.

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5.7B: Aerobic Hydrocarbon Oxidation

Learning Objectives

- Discuss the advantages of organisms that can undergo aerobic hydrocarbon oxidation

Microbes can utilize hydrocarbons via oxidation as an energy source.

Microbes can use many different carbon sources for energy. The best known and perhaps most common example is glucose. Microbes can utilize hydrocarbons via a stepwise oxidation of a hydrocarbon by oxygen produces water and, successively, an alcohol, an aldehyde or a ketone, a carboxylic acid, and then a peroxide. Note the presence of oxygen, thus defining this as aerobic hydrocarbon oxidation. There are examples of anaerobic hydrocarbon oxidation, which will not be discussed here. This is of special interest as many of the environment pollutants released by human industry are often hydrocarbon based. One of the best examples is oil spills. Understanding how microbes digest hydrocarbons has started the field of microbial biodegradation, a type of bioremediation. The goal of this is to find ways of using microbes to degrade hydrocarbon spills or waste into less dangerous byproducts such as alcohol.

Hydrocarbon utilizing microorganisms, mostly Cladosporium resinae and Pseudomonas aeruginosa, colloquially known as “HUM bugs,” are commonly present in jet fuel. They live in the water-fuel interface of the water droplets, form dark black/brown/green, gel-like mats, and cause microbial corrosion to plastic and rubber parts of the aircraft fuel system by consuming them, and to the metal parts by the means of their acidic metabolic products. They are also incorrectly called algae due to their appearance. FSII, which is added to the fuel, acts as a growth retardant for them. There are about 250 kinds of bacteria that can live in jet fuel, but fewer than a dozen are meaningfully harmful.

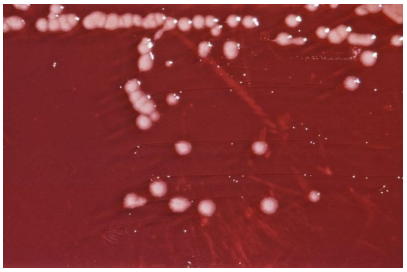

Figure: **Pseudomonas aeruginosa**: P. aeruginosa is capable of growth in diesel and jet fuel, where it is known as a hydrocarbon-using microorganism (or “HUM bug”), causing microbial corrosion. [3] It creates dark, gellish mats sometimes improperly called “algae” because of their appearance.

Biosurfactants are surface-active substances synthesized by living cells. Interest in microbial surfactants has been steadily increasing in recent years due to their diversity, environmentally friendly nature, possibility of large-scale production, selectivity, performance under extreme conditions, and potential applications in environmental protection. Biosurfactants enhance the emulsification of hydrocarbons, have the potential to solubilize hydrocarbon contaminants, and increase their availability for microbial degradation. The use of chemicals for the treatment of a hydrocarbon polluted site may contaminate the environment with their by-products, whereas biological treatment may efficiently destroy pollutants, while being biodegradable themselves. Therefore, biosurfactant-producing microorganisms may play an important role in the accelerated bioremediation of hydrocarbon-contaminated sites. These compounds can also be used in enhanced oil recovery and may be considered for other potential applications in environmental protection. Other applications include herbicides and pesticides formulations, detergents, healthcare and cosmetics, pulp and paper, coal, textiles, ceramic processing and food industries, uranium ore-processing, and mechanical dewatering of peat. Several microorganisms are known to synthesize surface-active agents; most of them are bacteria and yeasts. When grown on hydrocarbon substrate as the carbon source, these microorganisms synthesize a wide range of chemicals with surface activity, such as glycolipid, phospholipid, and others. These chemicals are synthesized to emulsify the hydrocarbon substrate and facilitate its transport into the cells. In some bacterial species such as Pseudomonas aeruginosa, biosurfactants are also involved in a group motility behavior called swarming motility.

Key Points

- Microbes in aerobic conditions can use hydrocarbons via oxidation of the hydrocarbon. This leads to byproducts such as water, alcohol, and peroxide.
- Many hydrocarbons are environmentally damaging, thus the break down of hydrocarbons by microbes is of special interest.

- HUM bugs can function as biosurfactants to facilitate the emulsification of hydrocarbons.

Key Terms

- **hydrocarbon**: A compound consisting only of carbon and hydrogen atoms.
- **biosurfactant**: Surface-active substances synthesized by living cells.
- **bioremediation**: The use of biological organisms, usually microorganisms, to remove contaminants, especially from polluted water.

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5.7C: The Pentose Phosphate Shunt

Learning Objectives

- Outline the two major phases of the pentose phosphate shunt: oxidative and non-oxidative phases

The pentose phosphate pathway (PPP; also called the phosphogluconate pathway and the hexose monophosphate shunt) is a process that breaks down glucose-6-phosphate into NADPH and pentoses (5-carbon sugars) for use in downstream biological processes. There are two distinct phases in the pathway: the oxidative phase and the non-oxidative phase. The first is the oxidative phase in which glucose-6-phosphate is converted to ribulose-5-phosphate. During this process two molecules of $NADP^+$are reduced to NADPH. The overall reaction for this process is:

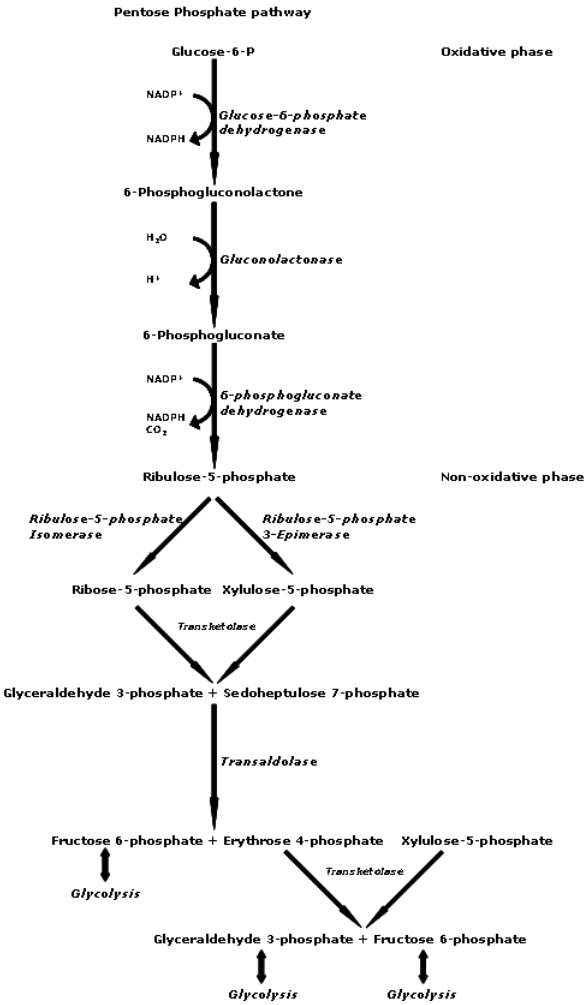

Figure: ***Figure 1 The Pentose Phosphate Pathway****: The pentose phosphate pathway generates reducing equivalents in the form of NADPH. It is used in reductive biosynthesis reactions within cells (e.g. fatty acid synthesis). It produces ribulose-5-phosphate, used in the synthesis of nucleotides. It also produces nucleic acids and erythrose-4-phosphate, used in the synthesis of aromatic amino acids.*

$$\text{Glucose 6-phosphate} + 2\ NADP^+ + H_2O \rightarrow \text{ribulose-5-phosphate} + 2\ NADPH + 2\ H^+ + CO_2$$

The second phase of this pathway is the non-oxidative synthesis of 5-carbon sugars. Depending on the body's state, ribulose-5-phosphate can reversibly isomerize to ribose-5-phosphate. Ribulose-5-phosphate can alternatively undergo a series of isomerizations as well as transaldolations and transketolations that result in the production of other pentose phosphates including fructose-6-phosphate, erythrose-4-phosphate, and glyceraldehyde-3-phosphate (both intermediates in glycolysis). These compounds are used in a variety of different biological processes including production of nucleotides and nucleic acids (ribose-5-phosphate), as well as synthesis of aromatic amino acids (erythrose-4-phosphate).

Glucose-6-phosphate dehydrogenase is the rate-controlling enzyme in this pathway. It is allosterically stimulated by $NADP^+$. NADPH-utilizing pathways, such as fatty acid synthesis, generate $NADP^+$, which stimulates glucose-6-phosphate dehydrogenase to produce more NADPH. In mammals, the PPP occurs exclusively in the cytoplasm; it is found to be most active in the liver, mammary gland, and adrenal cortex. The ratio of NADPH:$NADP^+$ is normally about 100:1 in liver cytosol, making the cytosol a highly-reducing environment.

The PPP is one of the three main ways the body creates molecules with reducing power, accounting for approximately 60% of NADPH production in humans. While the PPP does involve oxidation of glucose, its primary role is anabolic rather than catabolic, using the energy stored in NADPH to synthesize large, complex molecules from small precursors.

Additionally, NADPH can be used by cells to prevent oxidative stress. NADPH reduces glutathione via glutathione reductase, which converts reactive H_2O_2 into H_2O by glutathione peroxidase. For example, erythrocytes generate a large amount of NADPH through the pentose phosphate pathway to use in the reduction of glutathione.

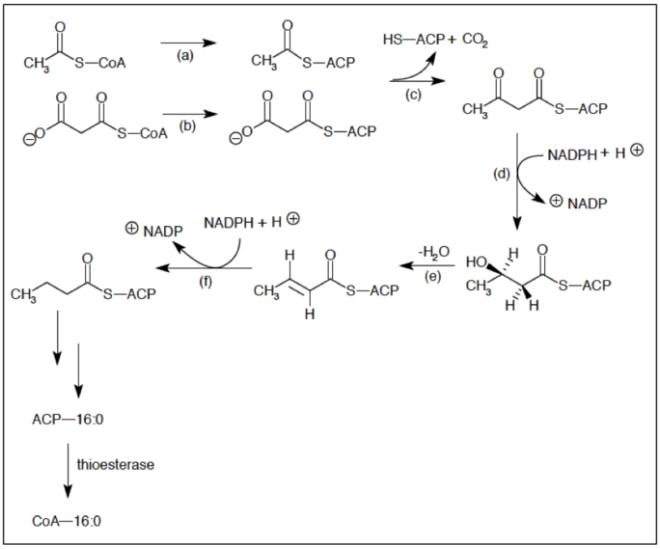

Figure: **Fatty Acid Synthesis**: Synthesis of Straight-Chain Saturated Fatty Acids

Key Points

- There are two distinct phases in the pathway: the oxidative phase and the non-oxidative phase.
- In the oxidative phase, two molecules of $NADP^+$ are reduced to NADPH, utilizing the energy from the conversion of glucose-6-phosphate into ribulose-5-phosphate. These NADPH molecules can then be used as an energy source in elsewhere in the cell.
- The non-oxidative phase generates 5-carbon sugars, which can be used in the synthesis of nucleotides, nucleic acids, and amino acids.
- The pentose phosphate pathway is an alternative to glycolysis.

Key Terms

- **glycolysis**: The cellular degradation of the simple sugar glucose to yield pyruvic acid and ATP as an energy source.
- **NADPH**: Nicotinamide adenine dinucleotide phosphate (NADP) carrying electrons and bonded with a hydrogen (H) ion; the reduced form of NADP+.
- **oxidative stress**: Damage caused to cells or tissue by reactive oxygen species.

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5.7D: Organic Acid Metabolism

Microbes can harness energy and carbon derived from organic acids by using a variety of dedicated metabolic enzymes.

LEARNING OBJECTIVES

Give examples of types of organic acid metabolism that are used by microorganisms for a sole source of energy

KEY TAKEAWAYS

Key Points

- Some microbes are capable of utilizing organic acids such as fatty acids, amino acids, or straight-chain unsaturated acids (e.g., lactate) as a sole source of energy.
- Metabolism of the organic acid formate is important in methylotrophic organisms. It is vital in the catabolism of C1 compounds (such as methanol).
- Many bacteria are capable of utilizing fatty acids as sole energy and carbon sources through the cyclic β-oxidation pathway, which ultimately yields acetyl-CoA.

Key Terms

- **fatty acid**: Any of a class of aliphatic carboxylic acids, of general formula CnH2n+1COOH, that occur combined with glycerol as animal or vegetable oils and fats. Only those with an even number of carbon atoms are normally found in natural fats.
- **acyl**: Any of class of organic radicals, RCO-, formed by the removal of a hydroxyl group from a carboxylic acid.
- **acetyl CoA**: Acetyl coenzyme A or acetyl-CoA is an important molecule in metabolism, used in many biochemical reactions. Its main function is to convey the carbon atoms within the acetyl group to the citric acid cycle (Krebs cycle) to be oxidized for energy production.

Organic Acid Metabolism

A great many organisms generate organic acids (such as lactate) as a byproduct of fermentation. Some microbes are capable of utilizing such compounds as a sole source of energy.

The most commonly metabolized organic acids are the carboxylic acids, which are organic acids containing at least one carboxyl (-COOH) group. The general formula of a carboxylic acid is R-COOH, where R is a monovalent functional group. Many types of carboxylic acids can be metabolized by microbes, including:

- Fatty acids (carboxylic acids with long acyl tails)
- Amino acids (the building blocks of proteins)
- Straight-chained, saturated acids (e.g., formate, acetate, and palmitate)

FORMATE METABOLISM

Formate metabolism is important in methylotrophic organisms. It is vital in the catabolism of C_1 compounds such as methanol (see the “Methylotrophy and Methanotrophy” atom for more information on C_1 compound utilization). Methylotrophic microbes convert single-carbon compounds to formaldehyde, which is oxidized to formate by formaldehyde dehydrogenase. Degradation of formate is then catalyzed by formate dehydrogenase (FDH), which oxidizes formate to ultimately yield CO_2. It permits the donation of electrons to a second substrate (such as NAD+) in the process. This is a critical late step in the hydrocarbon utilization pathway. The ability to metabolize formate is also critical in bacterial anaerobic metabolism, in which case formate is also oxidized by an FDH enzyme but the electrons are donated to cytochromes (proteins involved in electron transport).

FATTY ACID METABOLISM

Many bacteria are capable of utilizing fatty acids of various tail lengths as sole energy and carbon sources. This process requires the β-oxidation pathway, a cyclic process that catalyzes the sequential shortening of fatty acid acyl chains to the final product, acetyl-CoA. The step-by-step process occurs as follows:

1. Fatty acid chains are converted to enoyl-CoA (catalyzed by acyl-CoA dehydrogenase).
2. Enoyl-CoA is converted to 3-hydroxyacyl-CoA (catalyzed by enoyl-CoA hydratase).
3. 3-hydroxyacyl-CoA is converted to 3-ketoacyl-CoA (catalyzed by 3-hydroxyacyl-CoA dehydrogenase).

4. 3-ketoacyl-CoA is thiolated (by 3-ketoacyl-CoA thiolase) to yield one molecule of acetyl-CoA and a derivative of the original input fatty acid that is now shorter by two carbons.

The fatty acid chain that is left over after the thiolation step can then reenter the β-oxidation pathway, which can cycle until the fatty acid has been completely reduced to acetyl-CoA. Acertyl-CoA is the entry molecule for the TCA cycle. The TCA cycle is the process used by all aerobic organisms to generate energy.

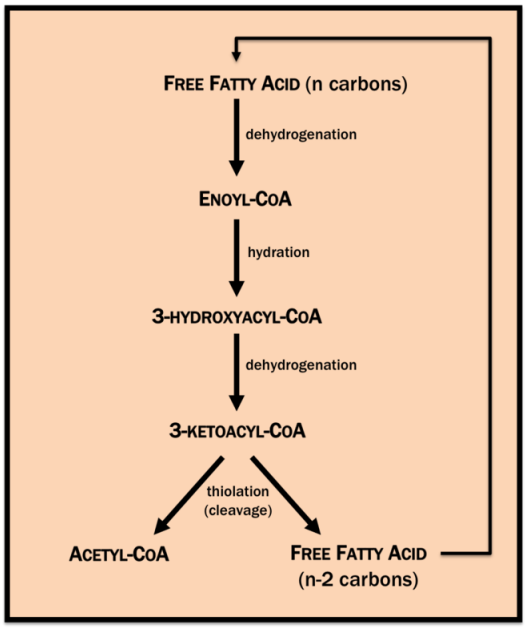

Figure: **β-oxidation of fatty acids**: Free fatty acids are broken down to acetyl-CoA by dedicated enzymes in the β-oxidation pathway.

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5.7E: Lipid Metabolism

Biological lipids, which are broken down and utilized though β-oxidation, represent a potent energy source.

Learning Objectives

- Outline the process of lipid metabolism, specifically beta-oxidation

Key Points

- In addition to their role as the primary component of cell membranes, lipids can be metabolized for use as a primary energy source.
- Lipid metabolism involves the degradation of fatty acids, which are fundamental biological molecules and the building blocks of more structurally complex lipids.
- In order to be metabolized by the cell, lipids are hydrolyzed to yield free fatty acids that then converted to acetyl-CoA through the β- oxidation pathway.
- One major feature of anaerobic digestion is the production of biogas (with the most useful component being methane), which can be used in generators for electricity production and/or in boilers for heating purposes.

Key Terms

- **carboxylic acid**: Any of a class of organic compounds containing a carboxyl functional group.
- **coenzyme A**: A coenzyme, formed from pantothenic acid and adenosine triphosphate, that is necessary for fatty acid synthesis and metabolism.

Lipid Metabolism

Lipids are universal biological molecules. Not only does this broad class of compounds represent the primary structural component of biological membranes in all organisms, they also serve a number of vital roles in microorganisms. Among these, lipids can be metabolized by microbes for use as a primary energy source. Although not stated explicitly, the “Organic Acid Metabolism” atom in this module introduces the concept of lipid metabolism by describing the process of fatty acid metabolism through β-oxidation. This atom will expand on the metabolic pathway that enables degradation and utilization of lipids. Fatty acids are the building blocks of lipids. They are made of a hydrocarbon chain of variable length that terminates with a carboxylic acid group (-COOH). The fatty acid structure (see below) is one of the most fundamental categories of biological lipids. It is commonly used as a building block of more structurally complex lipids (such as phospholipids and triglycerides). When metabolized, fatty acids yield large quantities of ATP, which is why these molecules are important energy sources. Lipids are an energy and carbon source. Before complex lipids can be used to produce energy, they must first be hydrolyzed. This requires the activity of hydrolytic enzymes called lipases, which release fatty acids from derivatives such as phospholipids. These fatty acids can then enter a dedicated pathway that promotes step-wise lipid processing that ultimately yields acetyl-CoA, a critical metabolite that conveys carbon atoms to the TCA cycle (aka Krebs cycle or citric acid cycle) to be oxidized for energy production.

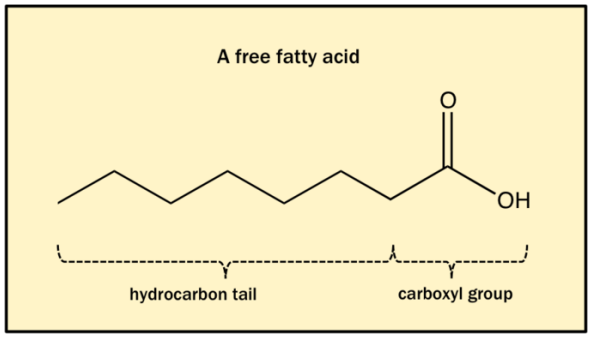

Figure: **An example of a fatty acid**: A fatty acid is a carboxylic acid with a long aliphatic tail that may be either saturated or unsaturated. The molecule shown here is the eight-carbon saturated fatty acid known as octanoic acid (or caprylic acid).

β-oxidation

The metabolic process by which fatty acids and their lipidic derivatives are broken down is called β-oxidation. This process bears significant similarity to the mechanism by which fatty acids are synthesized, except in reverse. In brief, the oxidation of lipids

proceeds as follows: two-carbon fragments are removed sequentially from the carboxyl end of the fatty acid after dehydrogenation, hydration, and oxidation to form a keto acid, which is then cleaved by thiolysis. The acetyl-CoA molecule liberated by this process is eventually converted into ATP through the TCA cycle.

β-oxidation can be broken down into a series of discrete steps:

1. Activation: Before fatty acids can be metabolized, they must be “activated. ” This activation step involves the addition of a coenzyme A (CoA) molecule to the end of a long-chain fatty acid, after which the activated fatty acid (fatty acyl -CoA) enters the β-oxidation pathway.
2. Oxidation: The initial step of β-oxidation is catalyzed by acyl-CoA dehydrogenase, which oxidizes the fatty acyl-CoA molecule to yield enoyl-CoA. As a result of this process, a trans double bond is introduced into the acyl chain.
3. Hydration: In the second step, enoyl-CoA hydratase hydrates the double bond introduced in the previous step, yielding an alcohol (-C-OH).
4. Oxidation: Hydroxyacyl-CoA dehydrogenase oxidizes the alcohol formed in the previous step to a carbonyl (-C=O).
5. Cleavage: A thiolase then cleaves off acetyl-CoA from the oxidized molecule, which also yields an acyl-CoA that is two carbons shorter than the original molecule that entered the β-oxidation pathway.

This cycle repeats until the fatty acid has been completely reduced to acetyl-CoA, which is fed through the TCA cycle to ultimately yield cellular energy in the form of ATP.

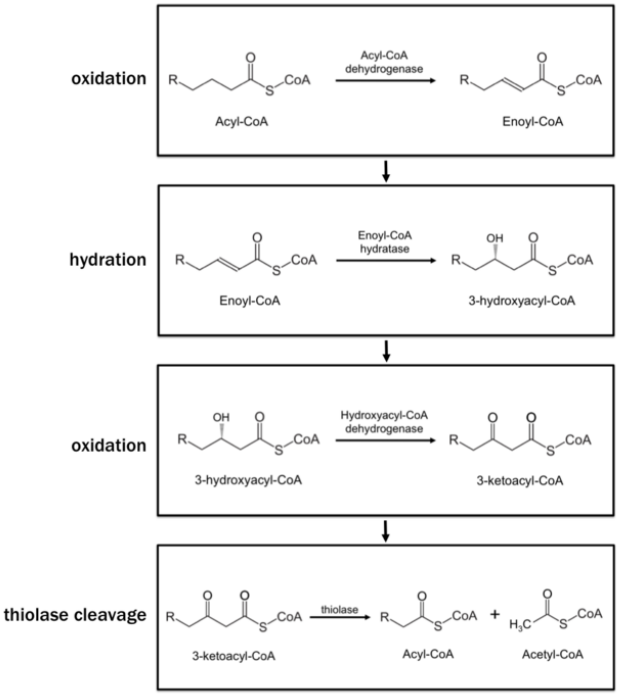

Figure: **β-oxidation**: The sequential steps of the β-oxidation pathway.

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5.7F: Connecting Proteins to Glucose Metabolism

Excess amino acids are converted into molecules that can enter the pathways of glucose catabolism.

Learning Objectives

- Describe the role played by proteins in glucose metabolism

Key Points

- Amino acids must be deaminated before entering any of the pathways of glucose catabolism: the amino group is converted to ammonia, which is used by the liver in the synthesis of urea.
- Deaminated amino acids can be converted into pyruvate, acetyl CoA, or some components of the citric acid cycle to enter the pathways of glucose catabolism.
- Several amino acids can enter the glucose catabolism pathways at multiple locations.

Key Terms

- **catabolism**: Destructive metabolism, usually including the release of energy and breakdown of materials.
- **keto acid**: Any carboxylic acid that also contains a ketone group.
- **deamination**: The removal of an amino group from a compound.

Metabolic pathways should be thought of as porous; that is, substances enter from other pathways and intermediates leave for other pathways. These pathways are not closed systems. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways. Proteins are a good example of this phenomenon. They can be broken down into their constituent amino acids and used at various steps of the pathway of glucose catabolism.

Proteins are hydrolyzed by a variety of enzymes in cells. Most of the time, the amino acids are recycled into the synthesis of new proteins or are used as precursors in the synthesis of other important biological molecules, such as hormones, nucleotides, or neurotransmitters. However, if there are excess amino acids, or if the body is in a state of starvation, some amino acids will be shunted into the pathways of glucose catabolism.

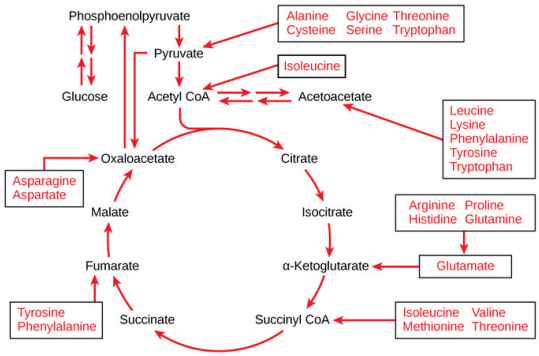

Figure: **Connection of Amino Acids to Glucose Metabolism Pathways**: The carbon skeletons of certain amino acids (indicated in boxes) are derived from proteins and can feed into pyruvate, acetyl CoA, and the citric acid cycle.

Each amino acid must have its amino group removed (deamination) prior to the carbon chain's entry into these pathways. When the amino group is removed from an amino acid, it is converted into ammonia through the urea cycle. The remaining atoms of the amino acid result in a keto acid: a carbon chain with one ketone and one carboxylic acid group. In mammals, the liver synthesizes urea from two ammonia molecules and a carbon dioxide molecule. Thus, urea is the principal waste product in mammals produced from the nitrogen originating in amino acids; it leaves the body in urine. The keto acid can then enter the citric acid cycle.

When deaminated, amino acids can enter the pathways of glucose metabolism as pyruvate, acetyl CoA, or several components of the citric acid cycle. For example, deaminated asparagine and aspartate are converted into oxaloacetate and enter glucose catabolism in the citric acid cycle. Deaminated amino acids can also be converted into another intermediate molecule before entering the pathways. Several amino acids can enter glucose catabolism at multiple locations.

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5.7G: Methylotrophy and Methanotrophy

Methylotrophs and methanotrophs are a diverse group of microorganisms that can derive energy from the metabolism of single-carbon compounds.

Learning Objectives

- Distinguish between methylotrophs and methanotrophs and their energy sources

Key Points

- Microbes with the ability to utilize single-carbon (C1) compounds (or multi-carbon compounds lacking carbon bonds) as the sole energy source for their growth are known as methylotrophs.
- Methanotrophs, a specific type of methylotroph, are able to metabolize methane as their only source of carbon and energy.
- Methylotrophs aerobically utilize C1 compounds by oxidizing them to yield formaldehyde, which in turn can either be used for energy or assimilated into biomass.

Key Terms

- **methylotroph**: Any organism that utilizes simple methyl compounds (such as methane or methanol) as a source of carbon and of energy.
- **monooxygenase**: Any oxygenase enzyme that catalyzes the incorporation of a single atom of molecular oxygen into a substrate, the other atom being reduced to water; active in the metabolism of many foreign compounds.
- **methanogenesis**: The generation of methane by anaerobic bacteria.

Methylotrophs

Multiple diverse microorganisms have evolved the intriguing ability to utilize single-carbon (C_1) compounds (e.g. methanol or methane) or multi-carbon compounds lacking carbon bonds (e.g. dimethyl ether and dimethylamine) as the sole energy source for their growth. Microbes with this capability are known as methylotrophs.

Methylotrophs, in general, aerobically utilize C_1 compounds by oxidizing them to yield formaldehyde. Formaldehyde, in turn, can either be "burned" for energy (by dissimilation to CO_2) or assimilated into biomass, allowing the cell to grow using molecules like methanol as a sole carbon source. Because methanol is more abundant, more easily purified, and cheaper than sugar carbon sources (e.g. glucose), methylotrophs are particularly useful in biotechnology for the production of amino acids, vitamins, recombinant proteins, single-cell proteins, co- enzymes, and cytochromes.

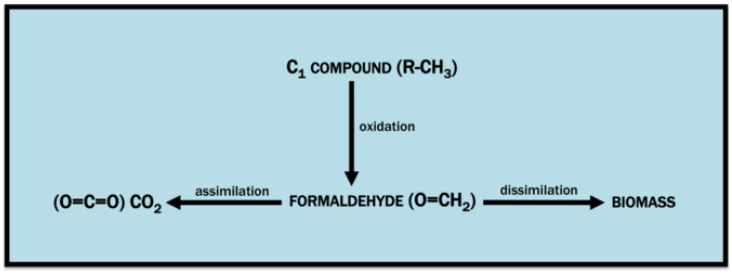

Figure: **Methylotrophy**: This is the general utilization pathway for C1 compounds. Molecules of this type are converted to formaldehyde by oxidation and ultimately used as a source of energy and carbon.

Here are examples of methylotrophs:

- Methanosarcina, which can both utilize and produce methane;
- Methylococcus capsulatus, which requires methane to survive; and
- Pichia pastoris, a biotechnologically important model organism that can use methanol as a carbon and energy source.

Methanotrophs

Some methylotrophs can degrade the greenhouse gas methane. Organisms of this type are referred to as methanotrophs. Methanotrophs are able to metabolize methane as their only source of carbon and energy. Most known methanotrophs are bacteria

that strictly require methane for growth (“obligate methanotrophs”). The fact that some methylotrophs can also make use of multi-carbon compounds distinguishes them from methanotrophs, which are usually fastidious methane and methanol oxidizers.

Methanotrophs occur mostly in soils. They are especially common near environments where methane is produced, such as:

- oceans
- mud
- marshes
- underground environments
- soils
- rice paddies
- landfills

Methanotrophs are of special interest to researchers studying global warming because they prevent a potential greenhouse gas (methane), far more potent than carbon dioxide, from being released into the atmosphere. Methanophilic (“methane-loving”) bacteria, therefore, are significant in the global methane budget.

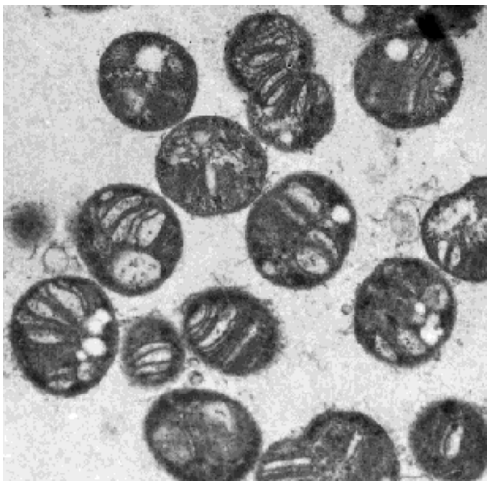

Figure: **Methylococcus capsulatus**: The Methylococcaceae have internal membranes (in the form of flattened discs) that contain pMMOs, which catalyze methane oxidation.

Methane Utilization

Methanotrophs oxidize methane by first initiating reduction of oxygen (O_2) to water (H_2O) and oxidation of methane (CH_4) to a more active species, methanol (CH_3OH), using oxidoreductase enzymes called methane monooxygenases (MMOs). Two types of MMO have been isolated from methanotrophs:

- soluble methane monooxygenase (sMMO), which is found in the cell cytoplasm.
- particulate methane monooxygenase (pMMO), which is found in the cell membrane.

Cells containing pMMO demonstrate higher growth capabilities and higher affinity for methane than cells that contain sMMO. Because pMMO is a membrane protein, cells that use it for methane metabolism characteristically have a system of internal membranes within which methane oxidation occurs.

As in the general case described above for methylotrophs, methanotrophs ultimately oxidize the methanol produced by MMOs to yield formaldehyde. The method of formaldehyde fixation differs between various methanotrophic organisms. This difference (along with variability in membrane structure) divides methanotrophs into several subgroups, such as the Methylococcaceae, Methylocystaceae, and Verrucomicrobiae. Although the mechanism by which it occurs is not entirely clear, it is also apparent that certain bacteria can utilize methane anaerobically by essentially running the methanogenesis pathway (normally used by methanogenic bacteria to produce methane) in reverse. This typically occurs in microbes dwelling in marine sediments where oxygen is scarce or altogether absent.

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SECTION OVERVIEW

5.8: Fermentation

Topic hierarchy

5.8A: Anaerobic Cellular Respiration

5.8B: Clostridial and Propionic Acid Fermentation

5.8C: Fermentation Without Substrate-Level Phosphorylation

5.8C: Syntrophy

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5.8A: Anaerobic Cellular Respiration

Learning Objectives

- Describe the process of anaerobic cellular respiration.

Anaerobic Cellular Respiration

The production of energy requires oxygen. The electron transport chain, where the majority of ATP is formed, requires a large input of oxygen. However, many organisms have developed strategies to carry out metabolism without oxygen, or can switch from aerobic to anaerobic cell respiration when oxygen is scarce.

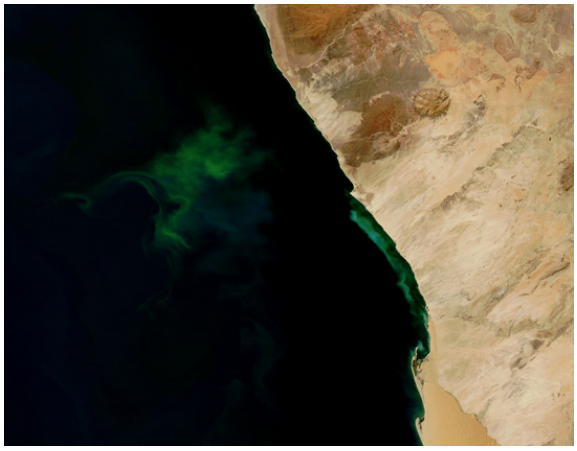

Figure: ***Anaerobic bacteria****: The green color seen in these coastal waters is from an eruption of hydrogen sulfide-producing bacteria. These anaerobic, sulfate-reducing bacteria release hydrogen sulfide gas as they decompose algae in the water.*

During cellular respiration, some living systems use an organic molecule as the final electron acceptor. Processes that use an organic molecule to regenerate NAD^+ from NADH are collectively referred to as fermentation. In contrast, some living systems use an inorganic molecule as a final electron acceptor. Both methods are called anaerobic cellular respiration, where organisms convert energy for their use in the absence of oxygen.

Certain prokaryotes, including some species of bacteria and archaea, use anaerobic respiration. For example, the group of archaea called methanogens reduces carbon dioxide to methane to oxidize NADH. These microorganisms are found in soil and in the digestive tracts of ruminants, such as cows and sheep. Similarly, sulfate-reducing bacteria and archaea, most of which are anaerobic, reduce sulfate to hydrogen sulfide to regenerate NAD^+ from NADH.

Eukaryotes can also undergo anaerobic respiration. Some examples include alcohol fermentation in yeast and lactic acid fermentation in mammals.

Lactic Acid Fermentation

The fermentation method used by animals and certain bacteria (like those in yogurt) is called lactic acid fermentation. This type of fermentation is used routinely in mammalian red blood cells and in skeletal muscle that has an insufficient oxygen supply to allow aerobic respiration to continue (that is, in muscles used to the point of fatigue). The excess amount of lactate in those muscles is what causes the burning sensation in your legs while running. This pain is a signal to rest the overworked muscles so they can recover. In these muscles, lactic acid accumulation must be removed by the blood circulation and the lactate brought to the liver for further metabolism. The chemical reactions of lactic acid fermentation are the following:

$$\text{Pyruvic acid} + \text{NADH} \leftrightarrow \text{lactic acid} + NAD^+$$

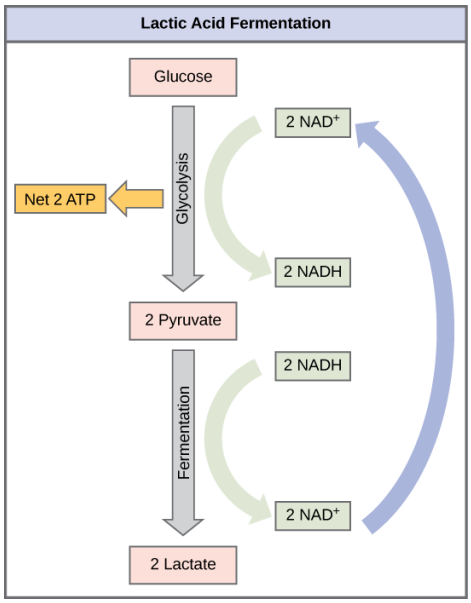

Figure: ***Lactic acid fermentation****: Lactic acid fermentation is common in muscle cells that have run out of oxygen.*

The enzyme used in this reaction is lactate dehydrogenase (LDH). The reaction can proceed in either direction, but the reaction from left to right is inhibited by acidic conditions. Such lactic acid accumulation was once believed to cause muscle stiffness, fatigue, and soreness, although more recent research disputes this hypothesis. Once the lactic acid has been removed from the muscle and circulated to the liver, it can be reconverted into pyruvic acid and further catabolized for energy.

Alcohol Fermentation

Another familiar fermentation process is alcohol fermentation, which produces ethanol, an alcohol. The use of alcohol fermentation can be traced back in history for thousands of years. The chemical reactions of alcoholic fermentation are the following (Note: CO_2 does not participate in the second reaction):

$$\text{Pyruvic acid} \rightarrow CO2 + \text{acetaldehyde} + NADH \rightarrow \text{ethanol} + NAD^+$$



Figure: ***Alcohol Fermentation****: Fermentation of grape juice into wine produces CO2 as a byproduct. Fermentation tanks have valves so that the pressure inside the tanks created by the carbon dioxide produced can be released.*

The first reaction is catalyzed by pyruvate decarboxylase, a cytoplasmic enzyme, with a coenzyme of thiamine pyrophosphate (TPP, derived from vitamin B_1 and also called thiamine). A carboxyl group is removed from pyruvic acid, releasing carbon dioxide as a gas. The loss of carbon dioxide reduces the size of the molecule by one carbon, making acetaldehyde. The second reaction is catalyzed by alcohol dehydrogenase to oxidize NADH to NAD^+ and reduce acetaldehyde to ethanol.

The fermentation of pyruvic acid by yeast produces the ethanol found in alcoholic beverages. Ethanol tolerance of yeast is variable, ranging from about 5 percent to 21 percent, depending on the yeast strain and environmental conditions.

Other Types of Fermentation

Various methods of fermentation are used by assorted organisms to ensure an adequate supply of NAD^+ for the sixth step in glycolysis. Without these pathways, that step would not occur and no ATP would be harvested from the breakdown of glucose.Other fermentation methods also occur in bacteria. Many prokaryotes are facultatively anaerobic. This means that they can switch between aerobic respiration and fermentation, depending on the availability of oxygen. Certain prokaryotes, like *Clostridia*, are obligate anaerobes. Obligate anaerobes live and grow in the absence of molecular oxygen. Oxygen is a poison to these microorganisms, killing them on exposure.

It should be noted that all forms of fermentation, except lactic acid fermentation, produce gas. The production of particular types of gas is used as an indicator of the fermentation of specific carbohydrates, which plays a role in the laboratory identification of the bacteria.

Key Points

- Anaerobic respiration is a type of respiration where oxygen is not used; instead, organic or inorganic molecules are used as final electron acceptors.
- Fermentation includes processes that use an organic molecule to regenerate NAD^+ from NADH.
- Types of fermentation include lactic acid fermentation and alcohol fermentation, in which ethanol is produced.
- All forms of fermentation except lactic acid fermentation produce gas, which plays a role in the laboratory identification of bacteria.
- Some types of prokaryotes are facultatively anaerobic, which means that they can switch between aerobic respiration and fermentation, depending on the availability of oxygen.

Key Terms

- **archaea**: A group of single-celled microorganisms. They have no cell nucleus or any other membrane-bound organelles within their cells.
- **anaerobic respiration**: A form of respiration using electron acceptors other than oxygen.
- **fermentation**: An anaerobic biochemical reaction. When this reaction occurs in yeast, enzymes catalyze the conversion of sugars to alcohol or acetic acid with the evolution of carbon dioxide.

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5.8B: Clostridial and Propionic Acid Fermentation

Learning Objectives

- Discuss the process of acidogenesis and the production of propionate

Four Stages of Anaerobic Digestion

Acidogenesis is the second stage in the four stages of anaerobic digestion: hydrolysis, acidogenesis, acetogenesis, and methanogenesis. Hydrolysis is a chemical reaction wherein particulates are solubilized and large polymers are converted into simpler monomers. Acidogenesis is a biological reaction wherein simple monomers are converted into volatile fatty acids. Acetogenes is a biological reaction wherein volatile fatty acids are converted into acetic acid, carbon dioxide, and hydrogen. Finally, methanogenesis is a biological reaction wherein acetates are converted into methane and carbon dioxide, and hydrogen is consumed.



Figure: **Biofuel production can come from plants, algae, and bacteria.**: Biohydrogen is defined as hydrogen produced biologically, most commonly by algae, bacteria, and archaea. Species of the Clostridium genus allow hydrogen production, a potential biofuel, in mixed cultures.

Anaerobic digestion is a complex biochemical process of mediated reactions undertaken by a consortium of microorganisms to convert organic compounds into methane and carbon dioxide. It is a stabilization process, reducing odor, pathogens, and mass reduction. Hydrolytic bacteria form a variety of reduced end-products from the fermentation of a given substrate.

One fundamental question in anaerobic digestion concerns the metabolic features that control carbon and electron flow. This flow is directed toward a reduced end-product during pure culture and mixed methanogenic cultures of hydrolytic bacteria. *Thermoanaerobium brockii* is a representative thermophilic, hydrolytic bacterium, which ferments glucose, via the Embden–Meyerhof Parnas Pathway.

Acidogenisis

Acidogenic activity was found in the early 20th century, but it was not until mid-1960s that the engineering of phases separation was assumed in order to improve the stability and waste digester treatment. In this phase, complex molecules (carbohydrates, lipids, and proteins) are depolymerized into soluble compounds by hydrolytic enzymes (cellulases, hemicellulases, amylases, lipases and proteases). The hydrolyzed compounds are fermented into volatile fatty acids (acetate, propionate, butyrate, and lactate), neutral compounds (ethanol, methanol), ammonia, hydrogen and carbon dioxide. Acetogenesis is one of the main reactions of this stage. In this reaction, the intermediary metabolites produced are metabolized to acetate, hydrogen, and carbonic gas by the three main groups of bacteria—homoacetogens, syntrophes, and sulphoreductors. For the acetic acid production are considered three kind of bacteria: Clostridium aceticum, *Acetobacter woodii*, and *Clostridium termoautotrophicum*.

In 1979, Winter and Wolfe demonstrated that *A. wodii* in syntrophic association with *Methanosarcina* produce methane and carbon dioxide from fructose, instead of three molecules of acetate. *C. thermoaceticum* and *C. formiaceticum* are able to reduce the carbonic gas to acetate, but they do not have hydrogenases to inhabilite the hydrogen use, so they can produce three molecules of acetate from fructose. Acetic acid is equally a co-metabolite of the organic substrates' fermentation (sugars, glycerol, lactic acid, etc.) by diverse groups of microorganisms, which produce different acids:

- propionic bacteria (propionate + acetate)

- *Clostridium* (butyrate + acetate)
- Enterobacteria (acetate + lactate)
- Hetero-fermentative bacteria (acetate, propionate, butyrate, valerate, etc.)

Key Points

- Acetogenesis is the third stage in the four stages of anaerobic digestion.
- Acetogenesis end products are acetate, hydrogen, and carbonic gas.
- Acetogenesis occurs in three main groups of bacteria: homoacetogens, syntrophes, and sulphoreductors.

Key Terms

- **acetogenesis**: The anaerobic production of acetic acid or acetate by bacteria.
- **metabolite**: Any substance produced by, or taking part in, a metabolic reaction.

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5.8C: Fermentation Without Substrate-Level Phosphorylation

Learning Objectives

- Give examples of various types of fermentation: homolactic, heterolactic and alcoholic

Fermentation is the process of extracting energy from the oxidation of organic compounds, such as carbohydrates, using an endogenous electron acceptor, which is usually an organic compound. In contrast, respiration is where electrons are donated to an exogenous electron acceptor, such as oxygen, via an electron transport chain. Fermentation is important in anaerobic conditions when there is no oxidative phosphorylation to maintain the production of ATP (adenosine triphosphate) by glycolysis.

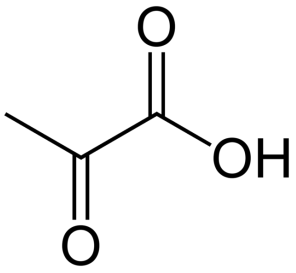

Figure: ***Pyruvic acid****: Pyruvic acid can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through acetyl-CoA. It can also be used to construct the amino acid alanine and be converted into ethanol. Pyruvic acid supplies energy to living cells through the citric acid cycle (also known as the Krebs cycle) when oxygen is present (aerobic respiration), and alternatively ferments to produce lactic acid when oxygen is lacking (fermentation).*

During fermentation, pyruvate is metabolised to various compounds. Homolactic fermentation is the production of lactic acid from pyruvate; alcoholic fermentation is the conversion of pyruvate into ethanol and carbon dioxide; and heterolactic fermentation is the production of lactic acid as well as other acids and alcohols. Fermentation does not necessarily have to be carried out in an anaerobic environment. For example, even in the presence of abundant oxygen, yeast cells greatly prefer fermentation to oxidative phosphorylation, as long as sugars are readily available for consumption (a phenomenon known as the Crabtree effect). The antibiotic activity of Hops also inhibits aerobic metabolism in Yeast.

Sugars are the most common substrate of fermentation, and typical examples of fermentation products are ethanol, lactic acid, lactose, and hydrogen. However, more exotic compounds can be produced by fermentation, such as butyric acid and acetone. Yeast carries out fermentation in the production of ethanol in beers, wines, and other alcoholic drinks, along with the production of large quantities of carbon dioxide. Fermentation occurs in mammalian muscle during periods of intense exercise where oxygen supply becomes limited, resulting in the creation of lactic acid.

Key Points

- Fermentation without substrate level phosphorylation uses an endogenous electron acceptor, which is usually an organic compound.
- Fermentation is important in anaerobic conditions when there is no oxidative phosphorylation to maintain the production of ATP (adenosine triphosphate) by glycolysis.
- During fermentation, pyruvate is metabolised to various compounds such as lactic acid, ethanol and carbon dioxide or other acids.

Key Terms

- **fermentation**: Any of many anaerobic biochemical reactions in which an enzyme (or several enzymes produced by a microorganism) catalyses the conversion of one substance into another; especially the conversion (using yeast) of sugars to alcohol or acetic acid with the evolution of carbon dioxide.
- **substrate**: a surface on which an organism grows or to which it is attached
- **oxidative phosphorylation**: Oxidative phosphorylation (or OXPHOS in short) is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP).
- **electron acceptor**: An electron acceptor is a chemical entity that accepts electrons transferred to it from another compound. It is an oxidizing agent that, by virtue of its accepting electrons, is itself reduced in the process.

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5.8C: Syntrophy

Learning Objectives

- Give examples of syntrophy in microbial metabolism

Syntrophy, or symbiosis, is the phenomenon involving one species living off the products of another species. For example, house dust mites live off human skin flakes. A healthy human being produces about 1 gram of skin flakes per day. These mites can also produce chemicals that stimulate the production of skin flakes. People can become allergic to these compounds. Another example are the many organisms that feast on feces or dung. A cow eats a lot of grass, the cellulose of which is transformed into lipids by micro-organisms in the cow's large intestine.



Figure: ***House dust mite****: The house dust mite (sometimes referred to by allergists as HDM) is a cosmopolitan guest in human habitation. Dust mites feed on organic detritus such as flakes of shed human skin and flourish in the stable environment of dwellings.*

These microorganisms cannot use the lipids because of a lack of dioxygen in the intestine, so the cow does not take up all the lipids produced. When the processed grass leaves the intestine as dung and comes into open air, many organisms, such as the dung beetle, feast on it. Yet another example is the community of micro-organisms in soil that live off leaf litter. Leaves typically last one year and are then replaced by new ones. These microorganisms mineralize the discarded leaves and release nutrients that are taken up by the plant. Such relationships are called reciprocal syntrophy because the plant lives off the products of micro-organisms. Many symbiotic relationships are based on syntrophy. Finally, anaerobic fermentation/methanogenesis is an example of a syntrophic relationship between different groups of microorganisms. Although fermentative bacteria are not strictly dependent on syntrophyic relationships, they still gain profit from the activities of the hydrogen-scavenging organisms. The fermentative bacteria gain maximum energy yield when protons are used as electron acceptor with concurrent H2 production.

Fermentation is a specific type of heterotrophic metabolism that uses organic carbon instead of oxygen as a terminal electron acceptor. This means that these organisms do not use an electron transport chain to oxidize NADH to NAD+ and therefore must have an alternative method of using this reducing power and maintaining a supply of NAD+ for the proper functioning of normal metabolic pathways (e.g. glycolysis). As oxygen is not required, fermentative organisms are anaerobic. Many organisms can use fermentation under anaerobic conditions and aerobic respiration when oxygen is present. These organisms are facultative anaerobes. To avoid the overproduction of NADH, obligately fermentative organisms usually do not have a complete citric acid cycle. Instead of using an ATP synthase as in respiration, ATP in fermentative organisms is produced by substrate-level phosphorylation where a phosphate group is transferred from a high-energy organic compound to ADP to form ATP. As a result of the need to produce high energy phosphate-containing organic compounds (generally in the form of CoA-esters) fermentative organisms use NADH and other cofactors to produce many different reduced metabolic by-products, often including hydrogen gas (H2). These reduced organic compounds are generally small organic acids and alcohols derived from pyruvate, the end product of glycolysis. Examples include ethanol, acetate, lactate, and butyrate. Fermentative organisms are very important industrially and are used to make many different types of food products. The different metabolic end products produced by each specific bacterial species are responsible for the different tastes and properties of each food.

The best studied example of syntrophy in microbial metabolism is the oxidation of fermentative end products (such as acetate, ethanol and butyrate) by organisms such as Syntrophomonas. Alone, the oxidation of butyrate to acetate and hydrogen gas is energetically unfavorable. However, when a hydrogenotrophic (hydrogen-using) methanogen is present the use of the hydrogen gas will significantly lower the concentration of hydrogen (down to 10−5 atm) and thereby shift the equilibrium of the butyrate oxidation reaction under standard conditions (ΔG^o) to non-standard conditions ($\Delta G'$). Because the concentration of one product is lowered, the reaction is "pulled" towards the products and shifted towards net energetically favorable conditions (for butyrate

oxidation: ΔG^{o}= +48.2 kJ/mol, but $\Delta G'$ = -8.9 kJ/mol at 10−5 atm hydrogen and even lower if also the initially produced acetate is further metabolized by methanogens). Conversely, the available free energy from methanogenesis is lowered from ΔG^{o}= -131 kJ/mol under standard conditions to $\Delta G'$ = -17 kJ/mol at 10−5 atm hydrogen. This is an example of intraspecies hydrogen transfer. In this way, low energy-yielding carbon sources can be used by a consortium of organisms to achieve further degradation and eventual mineralization of these compounds. These reactions help prevent the excess sequestration of carbon over geologic time scales, releasing it back to the biosphere in usable forms such as methane and CO2.

Key Points

- Anaerobic fermentation / methanogenesis is an example of a syntrophic relationship between different groups of microorganisms.
- Fermentation is a specific type of heterotrophic metabolism that uses organic carbon instead of oxygen as a terminal electron acceptor.
- The best studied example of syntrophy in microbial metabolism is the oxidation of fermentative end products (such as acetate, ethanol and butyrate) by organisms such as Syntrophomonas.

Key Terms

- **syntrophy**: The relationship between the individuals of different species (especially of bacteria) in which one or both benefit nutritionally from the presence of the other.
- **symbiosis**: A close, prolonged association between two or more organisms of different species, regardless of benefit to the members.
- **fermentation**: Any of many anaerobic biochemical reactions in which an enzyme (or several enzymes produced by a microorganism) catalyses the conversion of one substance into another; especially the conversion (using yeast) of sugars to alcohol or acetic acid with the evolution of carbon dioxide.

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SECTION OVERVIEW

5.9: Anaerobic Respiration

Topic hierarchy

5.9A: Electron Donors and Acceptors in Anaerobic Respiration

5.9B: Nitrate Reduction and Denitrification

5.9C: Sulfate and Sulfur Reduction

5.9D: Methanogenesis

5.9E: Proton Reduction

5.9F: Anoxic Hydrocarbon Oxidation

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5.9A: Electron Donors and Acceptors in Anaerobic Respiration

In anaerobic respiration, a molecule other than oxygen is used as the terminal electron acceptor in the electron transport chain.

Learning Objectives

- Describe various types of electron acceptors and donors including: nitrate, sulfate, hydrgoen, carbon dioxide and ferric iron

Key Points

- Both inorganic and organic compounds may be used as electron acceptors in anaerobic respiration. Inorganic compounds include sulfate (SO_4^{2-}), nitrate (NO_3^-), and ferric iron (Fe^{3+}). Organic compounds include DMSO.
- These molecules have a lower reduction potential than oxygen. Therefore, less energy is formed per molecule of glucose in anaerobic versus aerobic conditions.
- The reduction of certain inorganic compounds by anaerobic microbes is often ecologically significant.

Key Terms

- **anaerobic**: Without oxygen; especially of an environment or organism.
- **reduction**: A reaction in which electrons are gained and valence is reduced; often by the removal of oxygen or the addition of hydrogen.
- **anaerobic respiration**: metabolic reactions and processes that take place in the cells of organisms that use electron acceptors other than oxygen

Anaerobic respiration is the formation of ATP without oxygen. This method still incorporates the respiratory electron transport chain, but without using oxygen as the terminal electron acceptor. Instead, molecules such as sulfate (SO_4^{2-}), nitrate (NO_3^-), or sulfur (S) are used as electron acceptors. These molecules have a lower reduction potential than oxygen; thus, less energy is formed per molecule of glucose in anaerobic versus aerobic conditions.

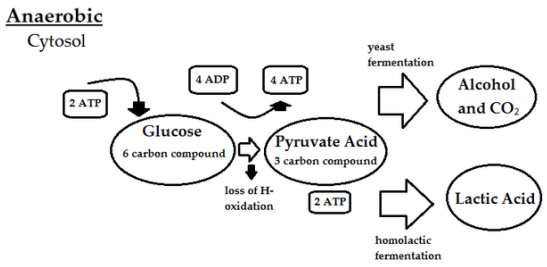

Figure: **Anaerobic Respiration**: A molecule other than oxygen is used as the terminal electron acceptor in anaerobic respiration.

Many different types of electron acceptors may be used for anaerobic respiration. Denitrification is the utilization of nitrate (NO_3^-) as the terminal electron acceptor. Nitrate, like oxygen, has a high reduction potential. This process is widespread, and used by many members of Proteobacteria. Many denitrifying bacteria can also use ferric iron (Fe^{3+}) and different organic electron acceptors.

Sulfate reduction uses sulfate (SO_2^{-4}) as the electron acceptor, producing hydrogen sulfide (H_2S) as a metabolic end product. Sulfate reduction is a relatively energetically poor process, and is used by many Gram negative bacteria found within the δ-Proteobacteria. It is also used in Gram-positive organisms related to Desulfotomaculum or the archaeon Archaeoglobus.

Sulfate reduction requires the use of electron donors, such as the carbon compounds lactate and pyruvate (organotrophic reducers), or hydrogen gas (lithotrophic reducers). Some unusual autotrophic sulfate-reducing bacteria, such as *Desulfotignum phosphitoxidans*, can use phosphite (HPO_3^-) as an electron donor. Others, such as certain *Desulfovibrio* species, are capable of sulfur disproportionation (splitting one compound into an electron donor and an electron acceptor) using elemental sulfur (S0), sulfite (SO_3^{-2}), and thiosulfate ($S_2O_3^{2-}$) to produce both hydrogen sulfide (H_2S) and sulfate (SO^{2-}).

Acetogenesis is a type of microbial metabolism that uses hydrogen (H_2) as an electron donor and carbon dioxide (CO_2) as an electron acceptor to produce acetate, the same electron donors and acceptors used in methanogenesis.

Ferric iron (Fe^{3+}) is a widespread anaerobic terminal electron acceptor used by both autotrophic and heterotrophic organisms. Electron flow in these organisms is similar to those in electron transport, ending in oxygen or nitrate, except that in ferric iron-reducing organisms the final enzyme in this system is a ferric iron reductase. Since some ferric iron-reducing bacteria (*e.g.G. metallireducens*) can use toxic hydrocarbons (*e.g.* toluene) as a carbon source, there is significant interest in using these organisms as bioremediation agents in ferric iron contaminated aquifers.

Other inorganic electron acceptors include the reduction of Manganic ion (Mn^{4+}) to manganous (Mn^{2+}), Selenate (SeO_4^{2-}) to selenite (SeO_3^{2-}) to selenium (Se), Arsenate (AsO_4^{3-}) to arsenite (AsO_3^{3-}), and Uranyl (UO_2^{2+}) to uranium dioxide (UO_2)

Organic compounds may also be used as electron acceptors in anaerobic respiration. These include the reduction of fumarate to succinate, Trimethylamine N-oxide (TMAO) to trimethylamine (TMA), and Dimethyl sulfoxide (DMSO) to Dimethyl sulfide (DMS).

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5.9B: Nitrate Reduction and Denitrification

Denitrification is a type of anaerobic respiration that uses nitrate as an electron acceptor.

Learning Objectives

- Outline the processes of nitrate reduction and denitrification and the organisms that utilize it

Key Points

- Denitrification generally proceeds through a stepwise reduction of some combination of the following intermediate forms: $NO_3^- \rightarrow NO_2^- \rightarrow NO + N_2O \rightarrow N_2$.
- Generally, several species of bacteria are involved in the complete reduction of nitrate to molecular nitrogen, and more than one enzymatic pathway has been identified in the reduction process.
- Complete denitrification is an environmentally significant process as some intermediates of denitrification (nitric oxide and nitrous oxide) are significant greenhouse gases that react with sunlight and ozone to produce nitric acid, a component of acid rain.

Key Terms

- **electron acceptor**: An electron acceptor is a chemical entity that accepts electrons transferred to it from another compound. It is an oxidizing agent that, by virtue of its accepting electrons, is itself reduced in the process.
- **eutrophication**: The process of becoming eutrophic.
- **facultative**: Not obligate; optional, discretionary or elective

In anaerobic respiration, denitrification utilizes nitrate (NO_3^-) as a terminal electron acceptor in the respiratory electron transport chain. Denitrification is a widely used process; many facultative anaerobes use denitrification because nitrate, like oxygen, has a high reduction potential

Denitrification is a microbially facilitated process involving the stepwise reduction of nitrate to nitrite (NO_2^-) nitric oxide (NO), nitrous oxide (N_2O), and, eventually, to dinitrogen (N_2) by the enzymes nitrate reductase, nitrite reductase, nitric oxide reductase, and nitrous oxide reductase. The complete denitrification process can be expressed as a redox reaction: $2\ NO^{3-} + 10\ e^- + 12\ H^+ \rightarrow N_2 + 6\ H_2O$.

Protons are transported across the membrane by the initial NADH reductase, quinones and nitrous oxide reductase to produce the electrochemical gradient critical for respiration. Some organisms (e.g. *E. coli*) only produce nitrate reductase and therefore can accomplish only the first reduction leading to the accumulation of nitrite. Others (e.g. *Paracoccus denitrificans* or *Pseudomonas stutzeri*) reduce nitrate completely. Complete denitrification is an environmentally significant process because some intermediates of denitrification (nitric oxide and nitrous oxide) are significant greenhouse gases that react with sunlight and ozone to produce nitric acid, a component of acid rain. Denitrification is also important in biological wastewater treatment, where it can be used to reduce the amount of nitrogen released into the environment, thereby reducing eutrophication.

Denitrification takes place under special conditions in both terrestrial and marine ecosystems. In general, it occurs where oxygen is depleted and bacteria respire nitrate as a substitute terminal electron acceptor. Due to the high concentration of oxygen in our atmosphere, denitrification only takes place in anaerobic environments where oxygen consumption exceeds the oxygen supply and where sufficient quantities of nitrate are present. These environments may include certain soils and groundwater, wetlands, oil reservoirs, poorly ventilated corners of the ocean, and in sea floor sediments.

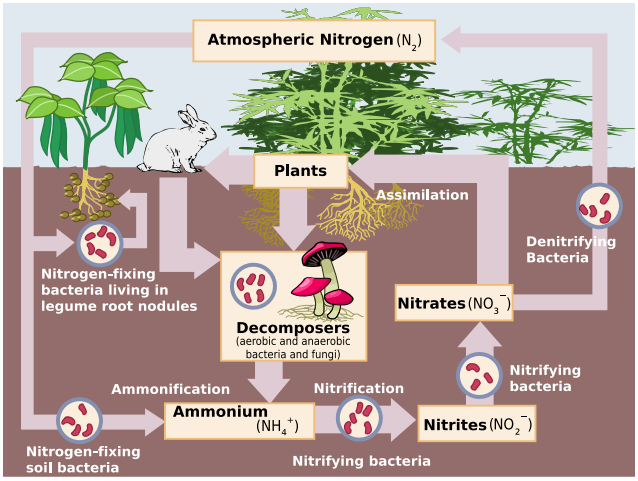

Figure: **The role of soil bacteria in the Nitrogen cycle**: Denitrification is an important process in maintaining ecosystems. Generally, denitrification takes place in environments depleted of oxygen.

Denitrification is performed primarily by heterotrophic bacteria (e.g. *Paracoccus denitrificans*), although autotrophic denitrifiers have also been identified (e.g., *Thiobacillus denitrificans*). Generally, several species of bacteria are involved in the complete reduction of nitrate to molecular nitrogen, and more than one enzymatic pathway have been identified in the reduction process.

Rhizobia are soil bacteria with the unique ability to establish a N_2-fixing symbiosis on legume roots. When faced with a shortage of oxygen, some *rhizobia* species are able to switch from O_2-respiration to using nitrates to support respiration.

The direct reduction of nitrate to ammonium (dissimilatory nitrate reduction) can be performed by organisms with the nrf- gene. This is a less common method of nitrate reduction than denitrification in most ecosystems. Other genes involved in denitrification include nir (nitrite reductase) and nos (nitrous oxide reductase), which are possessed by such organisms as *Alcaligenes faecalis*, *Alcaligenes xylosoxidans*, *Pseudomonas spp*, *Bradyrhizobium japonicum*, and *Blastobacter denitrificans*.

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5.9C: Sulfate and Sulfur Reduction

Sulfate reduction is a type of anaerobic respiration that utilizes sulfate as a terminal electron acceptor in the electron transport chain.

Learning Objectives

- Outline the process of sulfate and sulfur reduction including its various purposes

Key Points

- Sulfate reduction is a vital mechanism for bacteria and archaea living in oxygen-depleted, sulfate-rich environments.
- Sulfate reducers may be organotrophic, using carbon compounds, such as lactate and pyruvate as electron donors, or lithotrophic, and use hydrogen gas (H_2) as an electron donor.
- Before sulfate can be used as an electron acceptor, it must be activated by ATP -sulfurylase, which uses ATP and sulfate to create adenosine 5′-phosphosulfate (APS).
- Sulfate-reducing bacteria can be traced back to 3.5 billion years ago and are considered to be among the oldest forms of microorganisms, having contributed to the sulfur cycle soon after life emerged on Earth.
- Toxic hydrogen sulfide is one waste product of sulfate-reducing bactera, and is the source of the rotten egg odor.
- Sulfate-reducing bacteria may be utilized for cleaning up contaminated soils.

Key Terms

- **lithotrophic**: Obtains electrons for respiration from inorganic substrates.
- **organotrophic**: Obtains electrons for respiration from organic substrates.

Sulfate reduction is a type of anaerobic respiration that utilizes sulfate as a terminal electron acceptor in the electron transport chain. Compared to aerobic respiration, sulfate reduction is a relatively energetically poor process, though it is a vital mechanism for bacteria and archaea living in oxygen-depleted, sulfate-rich environments.

Many sulfate reducers are organotrophic, using carbon compounds, such as lactate and pyruvate (among many others) as electron donors, while others are lithotrophic, and use hydrogen gas (H_2) as an electron donor. Some unusual autotrophic sulfate-reducing bacteria (e.g., *Desulfotignum phosphitoxidans*) can use phosphite (HPO^{3-}) as an electron donor, whereas others (e.g., *Desulfovibrio sulfodismutans*, *Desulfocapsa thiozymogenes*, and *Desulfocapsa sulfoexigens*) are capable of sulfur disproportionation (splitting one compound into two different compounds, in this case an electron donor and an electron acceptor) using elemental sulfur (S0), sulfite (SO_3^{2-}), and thiosulfate ($S_2O_3^{2-}$) to produce both hydrogen sulfide (H_2S) and sulfate (SO_4^{2-}).

Before sulfate can be used as an electron acceptor, it must be activated. This is done by the enzyme ATP-sulfurylase, which uses ATP and sulfate to create adenosine 5′-phosphosulfate (APS). APS is subsequently reduced to sulfite and AMP. Sulfite is then further reduced to sulfide, while AMP is turned into ADP using another molecule of ATP. The overall process, thus, involves an investment of two molecules of the energy carrier ATP, which must to be regained from the reduction.

All sulfate-reducing organisms are strict anaerobes. Because sulfate is energetically stable, it must be activated by adenylation to form APS (adenosine 5′-phosphosulfate) to form APS before it can be metabolized, thereby consuming ATP. The APS is then reduced by the enzyme APS reductase to form sulfite (SO_3^{2-}) and AMP. In organisms that use carbon compounds as electron donors, the ATP consumed is accounted for by fermentation of the carbon substrate. The hydrogen produced during fermentation is actually what drives respiration during sulfate reduction.

Sulfate-reducing bacteria can be traced back to 3.5 billion years ago and are considered to be among the oldest forms of microorganisms, having contributed to the sulfur cycle soon after life emerged on Earth. Sulfate-reducing bacteria are common in anaerobic environments (such as seawater, sediment, and water rich in decaying organic material) where they aid in the degradation of organic materials. In these anaerobic environments, fermenting bacteria extract energy from large organic molecules; the resulting smaller compounds (such as organic acids and alcohols) are further oxidized by acetogens, methanogens, and the competing sulfate-reducing bacteria.

Many bacteria reduce small amounts of sulfates in order to synthesize sulfur-containing cell components; this is known as assimilatory sulfate reduction. By contrast, sulfate-reducing bacteria reduce sulfate in large amounts to obtain energy and expel the resulting sulfide as waste; this is known as “dissimilatory sulfate reduction. ” Most sulfate-reducing bacteria can also reduce other

oxidized inorganic sulfur compounds, such as sulfite, thiosulfate, or elemental sulfur (which is reduced to sulfide as hydrogen sulfide).

Toxic hydrogen sulfide is one waste product of sulfate-reducing bacteria; its rotten egg odor is often a marker for the presence of sulfate-reducing bacteria in nature. Sulfate-reducing bacteria are responsible for the sulfurous odors of salt marshes and mud flats. Much of the hydrogen sulfide will react with metal ions in the water to produce metal sulfides. These metal sulfides, such as ferrous sulfide (FeS), are insoluble and often black or brown, leading to the dark color of sludge. Thus, the black color of sludge on a pond is due to metal sulfides that result from the action of sulfate-reducing bacteria.



Figure: **Black sludge**: The black color of this pond is due to metal sulfides that result from the action of sulfate-reducing bacteria.

Some sulfate-reducing bacteria play a role in the anaerobic oxidation of methane (CH_4+ $SO4^{2-}$ → HCO_3– + HS– + H_2O). An important fraction of the methane formed by methanogens below the seabed is oxidized by sulfate-reducing bacteria in the transition zone separating the methanogenesis from the sulfate reduction activity in the sediments.This process is also considered a major sink for sulfate in marine sediments. In hydrofracturing fluids used to frack shale formations to recover methane (shale gas), biocide compounds are often added to water to inhibit the microbial activity of sulfate-reducing bacteria in order to avoid anaerobic methane oxidation and to minimize potential production loss.

Sulfate-reducing bacteria often create problems when metal structures are exposed to sulfate-containing water. The interaction of water and metal creates a layer of molecular hydrogen on the metal surface. Sulfate-reducing bacteria oxidize this hydrogen, creating hydrogen sulfide, which contributes to corrosion. Hydrogen sulfide from sulfate-reducing bacteria also plays a role in the biogenic sulfide corrosion of concrete, and sours crude oil.

Sulfate-reducing bacteria may be utilized for cleaning up contaminated soils; some species are able to reduce hydrocarbons, such as benzene, toluene, ethylbenzene, and xylene. Sulfate-reducing bacteria may also be a way to deal with acid mine waters.

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5.9D: Methanogenesis

Methanogenesis is a form of anaerobic respiration that uses carbon as a electron acceptor and results in the production of methane.

Learning Objectives

- Recognize the characteristics associated with methanogenesis

Key Points

- Carbon dioxide or acetic acid are the most commonly used electron acceptor in methanogenesis.
- Microbes capable of producing methane are called methanogens. They have been identified only from the domain Archaea – a group that is phylogenetically distinct from eukaryotes and bacteria.
- The production of methane is an important and widespread form of microbial metabolism. In most environments, it is the final step in the decomposition of biomass.
- Methane is a major greenhouse gas. The average cow emits around 250 liters of methane a day as a result of the breakdown of cellulose by methanogens. Therefore, the large scale raising of cattle for meat is a considerable contributor to global warming.

Key Terms

- **methanethiol**: A colourless gas, a thiol with a smell like rotten cabbage, found naturally in plants and animals.
- **cofactor**: A substance, especially a coenzyme or a metal, that must be present for an enzyme to function.
- **fermentation**: Any of many anaerobic biochemical reactions in which an enzyme (or several enzymes produced by a microorganism) catalyses the conversion of one substance into another; especially the conversion (using yeast) of sugars to alcohol or acetic acid with the evolution of carbon dioxide.

Methanogenesis, or biomethanation, is a form of anaerobic respiration that uses carbon as the terminal electron acceptor, resulting in the production of methane. The carbon is sourced from a small number of low molecular weight organic compounds, such as carbon dioxide, acetic acid, formic acid (formate), methanol, methylamines, dimethyl sulfide, and methanethiol. The two best described pathways of methanogenesis use carbon dioxide or acetic acid as the terminal electron acceptor:

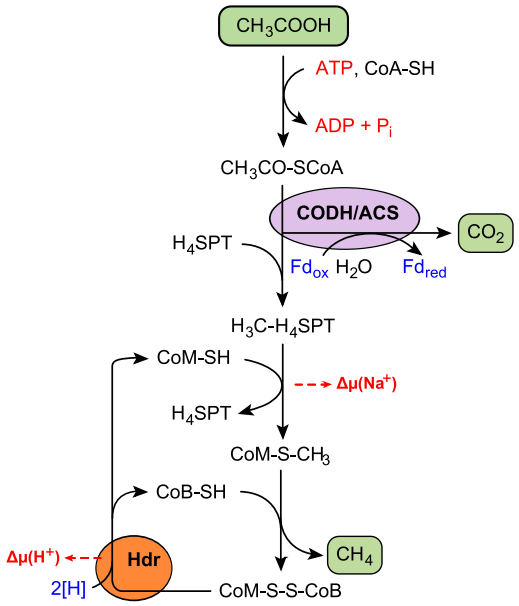

Figure: **Methanogenesis of acetate**: Acetate is broken down to methane by methanogenesis, a type of anaerobic respiration.

$CO_2 + 4\ H_2 \rightarrow CH_4 + 2H_2O$

$CH_3COOH \rightarrow CH_4 + CO_2$

The biochemistry of methanogenesis is relatively complex. It involves the coenzymes and cofactors F420, coenzyme B, coenzyme M, methanofuran, and methanopterin.

Microbes capable of producing methane are called methanogens. They have been identified only from the domain Archaea – a group that is phylogenetically distinct from eukaryotes and bacteria – though many live in close association with anaerobic bacteria. The production of methane is an important and widespread form of microbial metabolism, and in most environments, it is the final step in the decomposition of biomass.

During the decay process, electron acceptors (such as oxygen, ferric iron, sulfate, and nitrate) become depleted, while hydrogen (H2), carbon dioxide, and light organics produced by fermentation accumulate. During advanced stages of organic decay, all electron acceptors become depleted except carbon dioxide, which is a product of most catabolic processes. It is not depleted like other potential electron acceptors.

Only methanogenesis and fermentation can occur in the absence of electron acceptors other than carbon. Fermentation only allows the breakdown of larger organic compounds, and produces small organic compounds. Methanogenesis effectively removes the semi-final products of decay: hydrogen, small organics, and carbon dioxide. Without methanogenesis, a great deal of carbon (in the form of fermentation products) would accumulate in anaerobic environments.

Methanogenesis also occurs in the guts of humans and other animals, especially ruminants. In the rumen, anaerobic organisms, including methanogens, digest cellulose into forms usable by the animal. Without these microorganisms, animals such as cattle would not be able to consume grass. The useful products of methanogenesis are absorbed by the gut. Methane is released from the animal mainly by belching (eructation). The average cow emits around 250 liters of methane per day. Some, but not all, humans emit methane in their flatus!

Some experiments even suggest that leaf tissues of living plants emit methane, although other research indicates that the plants themselves do not actually generate methane; they are just absorbing methane from the soil and then emitting it through their leaf tissues. There may still be some unknown mechanism by which plants produce methane, but that is by no means certain.

Methane is one of the earth's most important greenhouse gases, with a global warming potential 25 times greater than carbon dioxide (averaged over 100 years). Therefore, the methane produced by methanogenesis in livestock is a considerable contributor to global warming.

Methanogenesis can also be beneficially exploited. It is the primary pathway that breaks down organic matter in landfills (which can release large volumes of methane into the atmosphere if left uncontrolled), and can be used to treat organic waste and to produce useful compounds. Biogenic methane can be collected and used as a sustainable alternative to fossil fuels.

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5.9E: Proton Reduction

Anaerobic respiration utilizes highly reduced species – such as a proton gradient – to establish electrochemical membrane gradients.

Learning Objectives

- Outline the role of the proton motive force in metabolism

Key Points

- In denitrification, protons are transported across the membrane by the initial NADH reductase, quinones, and nitrous oxide reductase to produce the electrochemical gradient critical for respiration.
- An electrochemical gradient represents one of the many interchangeable forms of potential energy through which energy may be conserved. In biological processes, the direction an ion moves by diffusion or active transport across a membrane is determined by the electrochemical gradient.
- In mitochondria and chloroplasts, proton gradients are used to generate a chemiosmotic potential that is also known as a proton motive force.

Key Terms

- **phosphorylation**: The process of transferring a phosphate group from a donor to an acceptor; often catalysed by enzymes

Proton Gradients in Reductive Metabolism

Biological energy is frequently stored and released by means of redox reactions, or the transfer of electrons. Reduction occurs when an oxidant gains an electron. Photosynthesis involves the reduction of carbon dioxide into sugars and the oxidation of water into molecular oxygen. The reverse reaction, respiration, oxidizes sugars (loses an electron) to produce carbon dioxide and water. As intermediate steps, the reduced carbon compounds are used to reduce nicotinamide adenine dinucleotide (NAD+), which then contributes to the creation of a proton gradient. This then drives the synthesis of adenosine triphosphate (ATP) and is maintained by the reduction of oxygen, or alternative receptors for anaerobic respiration. In animal cells, the mitochondria performs similar functions.

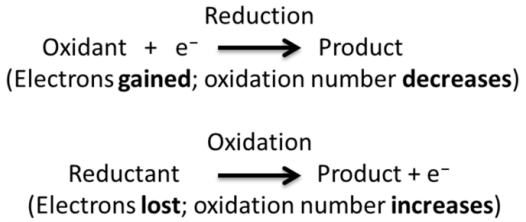

Figure: **The Basics of Redox**: In every redox reaction you have two halves: reduction and oxidation.

An electrochemical gradient represents one of the many interchangeable forms of potential energy through which energy may be conserved. In biological processes, the direction an ion moves by diffusion or active transport across a membrane is determined by the electrochemical gradient. In the mitochondria and chloroplasts, proton gradients are used to generate a chemiosmotic potential that is also known as a proton motive force. This potential energy is used for the synthesis of ATP by phosphorylation. An electrochemical gradient has two components. First, the electrical component is caused by a charge difference across the lipid membrane. Second, a chemical component is caused by a differential concentration of ions across the membrane. The combination of these two factors determines the thermodynamically favorable direction for an ion's movement across a membrane. The electrochemical potential difference between the two sides of the membrane in mitochondria, chloroplasts, bacteria, and other membranous compartments that engage in active transport involving proton pumps, is at times called a chemiosmotic potential or proton motive force.

In respiring bacteria under physiological conditions, ATP synthase, in general, runs in the opposite direction, creating ATP while using the proton motive force created by the electron transport chain as a source of energy. The overall process of creating energy in this fashion is termed oxidative phosphorylation. The same process takes place in the mitochondria, where ATP synthase is located in the inner mitochondrial membrane, so that F1 part sticks into the mitochondrial matrix where ATP synthesis takes place.

Cellular respiration (both aerobic and anaerobic) utilizes highly reduced species such as NADH and FADH2 to establish an electrochemical gradient (often a proton gradient) across a membrane, resulting in an electrical potential or ion concentration difference across the membrane. The reduced species are oxidized by a series of respiratory integral membrane proteins with sequentially increasing reduction potentials, the final electron acceptor being oxygen (in aerobic respiration) or another species (in anaerobic respiration). The membrane in question is the inner mitochondrial membrane in eukaryotes and the cell membrane in prokaryotes. A proton motive force or pmf drives protons down the gradient (across the membrane) through the proton channel of ATP synthase. The resulting current drives ATP synthesis from ADP and inorganic phosphate.

Proton reduction is important for setting up electrochemical gradients for anaerobic respiration. For example, in denitrification, protons are transported across the membrane by the initial NADH reductase, quinones, and nitrous oxide reductase to produce the electrochemical gradient critical for respiration. In organisms that use hydrogen as an energy source, hydrogen is oxidized by a membrane-bound hydrogenase causing proton pumping via electron transfer to various quinones and cytochromes. Sulfur oxidation is a two step process that occurs because energetically sulfide is a better electron donor than inorganic sulfur or thiosulfate, allowing for a greater number of protons to be translocated across the membrane.

In contrast, fermentation does not utilize an electrochemical gradient. Instead, it only uses substrate-level phosphorylation to produce ATP. The electron acceptor NAD+ is regenerated from NADH formed in oxidative steps of the fermentation pathway by the reduction of oxidized compounds. These oxidized compounds are often formed during the fermentation pathway itself, but may also be external. For example, in homofermentative lactic acid bacteria, NADH formed during the oxidation of glyceraldehyde-3-phosphate is oxidized back to NAD+ by the reduction of pyruvate to lactic acid at a later stage in the pathway. In yeast, acetaldehyde is reduced to ethanol.

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5.9F: Anoxic Hydrocarbon Oxidation

Anoxic hydrocarbon oxidation can be used to degrade toxic hydrocarbons, such as crude oil, in anaerobic environments.

Learning Objectives

- Describe the process of anoxic hydrocarbon oxidation in regards to marine environments

Key Points

- Hydrocarbons are organic compounds consisting entirely of hydrogen and carbon.
- The majority of hydrocarbons occur naturally in crude oil, where decomposed organic matter provides an abundance of carbon and hydrogen. The combustion of hydrocarbons is the primary energy source for current civilizations.
- Anaerobic oxidation of methane (AOM) is a microbial process that occurs in anoxic marine sediments. AOM is considered to be a very important process, reducing the emission of methane (a greenhouse gas) from the ocean into the atmosphere by up to 90%.

Key Terms

- **methanotrophic**: The ability to metabolize methane as an only source of carbon and energy.
- **syntrophic**: When one species lives off the products of another species.
- **anoxic**: Lacking oxygen.

Hydrocarbons are organic compounds consisting entirely of hydrogen and carbon. The majority of hydrocarbons occur naturally in crude oil, where decomposed organic matter provides an abundance of carbon and hydrogen. The combustion of hydrocarbons is the primary energy source for current civilizations.

Crude oil contains aromatic compounds that are toxic to most forms of life. Their release into the environment by human spills and natural seepages can have detrimental effects. Marine environments are especially vulnerable. Despite its toxicity, a considerable fraction of crude oil entering marine systems is eliminated by the hydrocarbon-degrading activities of microbial communities. Although it was once thought that hydrocarbon compounds could only be degraded in the presence of oxygen, the discovery of anaerobic hydrocarbon-degrading bacteria and pathways show that the anaerobic degradation of hydrocarbons occurs naturally.



Figure: **Contaminated soil**: Microbes may be used to degrade toxic hydrocarbons in anaerobic environments.

The facultative denitrifying proteobacteria *Aromatoleum aromaticum* strain EbN1 was the first to be determined as an anaerobic hydrocarbon degrader, using toluene or ethylbenzene as substrates. Some sulfate-reducing bacteria can reduce hydrocarbons such as benzene, toluene, ethylbenzene, and xylene, and have been used to clean up contaminated soils. The genome of the iron-reducing and hydrocarbon degrading species *Geobacter metallireducens* was recently determined.

Anaerobic oxidation of methane (AOM) is a microbial process that occurs in anoxic marine sediments. During this process, the hydrocarbon methane is oxidized with sulfate as the terminal electron acceptor: $CH_4 + SO_4^{2-} \rightarrow HCO^{3-} + HS^- + H_2O$. It is believed that AOM is mediated by a syntrophic aggregation of methanotrophic archaea and sulfate-reducing bacteria, although the exact mechanisms of this syntrophic relationship are still poorly understood. AOM is considered to be a very important process in reducing the emission of methane (a greenhouse gas) from the ocean into the atmosphere. It is estimated that almost 90% of all the methane that arises from marine sediments is oxidized anaerobically by this process. Recent investigations have shown that some syntrophic pairings are able to oxidize methane with nitrate instead of sulfate.

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SECTION OVERVIEW

5.10: Chemolithotrophy

Topic hierarchy

5.10A: The Energetics of Chemolithotrophy

5.10B: Hydrogen Oxidation

5.10C: Oxidation of Reduced Sulfur Compounds

5.10D: Iron Oxidation

5.10E: Nitrification

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5.10H: Polycyclic Aromatic Hydrocarbons

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5.10A: The Energetics of Chemolithotrophy

Learning Objectives

- Outline the characteristics associated with chemolithotrophs

A lithotroph is an organism that uses an inorganic substrate (usually of mineral origin) to obtain reducing equivalents for use in biosynthesis (e.g., carbon dioxide fixation) or energy conservation via aerobic or anaerobic respiration. Known chemolithotrophs are exclusively microbes; no known macrofauna possesses the ability to utilize inorganic compounds as energy sources. Macrofauna and lithotrophs can form symbiotic relationships, in which case the lithotrophs are called “prokaryotic symbionts”. An example of this is chemolithotrophic bacteria in deep sea worms or plastids, which are organelles within plant cells that may have evolved from photolithotrophic cyanobacteria-like organisms.

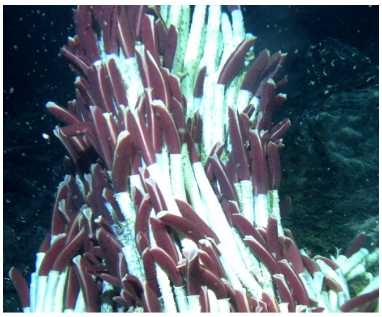

Figure: ***Gollner Riftia pachyptila****: Giant tube worms (Riftia pachyptila have an organ containing chemosynthetic bacteria instead of a gut.*

Chemotrophs are organisms that obtain energy through the oxidation of electron donors in their environments. These molecules can be organic (chemoorganotrophs) or inorganic (chemolithotrophs). The chemotroph designation is in contrast to phototrophs, which utilize solar energy. Chemotrophs can be either autotrophic or heterotrophic. Chemoautotrophs generally fall into several groups: methanogens, halophiles, sulfur oxidizers and reducers, nitrifiers, anammox bacteria, and thermoacidophiles. Chemolithotrophic growth could be dramatically fast, such as Thiomicrospira crunogena with a doubling time around one hour.

In chemolithotrophs, the compounds – the electron donors – are oxidized in the cell, and the electrons are channeled into respiratory chains, ultimately producing ATP. The electron acceptor can be oxygen (in aerobic bacteria), but a variety of other electron acceptors, organic and inorganic, are also used by various species. Unlike water, the hydrogen compounds used in chemosynthesis are high in energy. Other lithotrophs are able to directly utilize inorganic substances, e.g., iron, hydrogen sulfide, elemental sulfur, or thiosulfate, for some or all of their energy needs.

Key Points

- Chemotrophs are organisms that obtain energy by the oxidation of electron donors in their environments. These molecules can be organic (chemoorganotrophs) or inorganic (chemolithotrophs).
- In chemolithotrophs, the compounds – the electron donors – are oxidized in the cell, and the electrons are channeled into respiratory chains, ultimately producing ATP.
- The electron acceptor can be oxygen (in aerobic bacteria), but a variety of other electron acceptors, organic and inorganic, are also used by various species.

Key Terms

- **chemolithotroph**: chemoautotroph
- **symbiont**: An organism that lives in a symbiotic relationship; a symbiote.
- **chemotroph**: an organism that obtains energy by the oxidation of electron-donating molecules in the environment
- **lithotroph**: An organism that obtains its energy from inorganic compounds (such as ammonia) via electron transfer.

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5.10B: Hydrogen Oxidation

Learning Objectives

- Discuss the process of hydrogen oxidation in organisms that use hydrogen aerobically

Chemolithotrophy is a type of metabolism where energy is obtained from the oxidation of inorganic compounds. Most chemolithotrophic organisms are also autotrophic. There are two major objectives to chemolithotrophy: the generation of energy (via ATP) and the generation of reducing power (via NADH). Hydrogen oxidizing bacteria (sometimes called **Knallgas-bacteria**) are bacteria that oxidize hydrogen. These bacteria include *Hydrogenobacter thermophilus*, *Hydrogenovibrio marinus*, and *Helicobacter pylori*. There are both Gram positive and Gram negative knallgas bacteria.

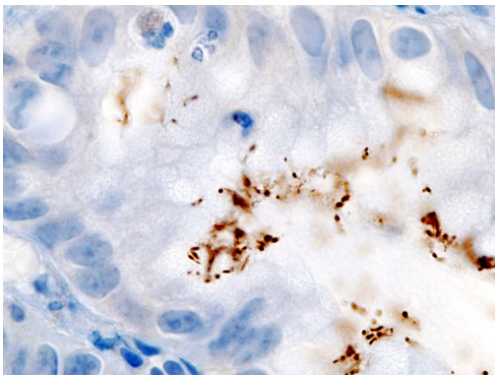

Figure: ***Immunohistochemical staining of H. pylori from a gastric biopsy****: Colonization with H. pylori is not a disease in and of itself, but a condition associated with a number of disorders of the upper gastrointestinal tract. Testing for H. pylori is recommended if there is peptic ulcer disease, low grade gastric MALT lymphoma, after endoscopic resection of early gastric cancer, if there are first degree relatives with gastric cancer, and in certain cases of dyspepsia, not routinely.*

Most grow best under microaerophilic conditions. They do this because the hydrogenase enzyme used in hydrogen oxidation is inhibited by the presence of oxygen, but oxygen is still needed as a terminal electron acceptor.

Many organisms are capable of using hydrogen (H_2) as a source of energy. While there are several mechanisms of anaerobic hydrogen oxidation (e.g. sulfate reducing- and acetogenic bacteria), hydrogen can also be used as an energy source aerobically. In these organisms, hydrogen is oxidized by a membrane-bound hydrogenase causing proton pumping via electron transfer to various quinones and cytochromes. In many organisms, a second cytoplasmic hydrogenase is used to generate reducing power in the form of NADH, which is subsequently used to fix carbon dioxide via the Calvin cycle. Hydrogen-oxidizing organisms, such as *Cupriavidus necator* (formerly *Ralstonia eutropha*), often inhabit oxic-anoxic interfaces in nature to take advantage of the hydrogen produced by anaerobic fermentative organisms while still maintaining a supply of oxygen.

Helicobacter pylori (H. pylori), previously named *Campylobacter pyloridis*, is a Gram-negative, microaerophilic bacterium found in the stomach. It was identified in 1982 by Barry Marshall and Robin Warren. They found that it was present in patients with chronic gastritis and gastric ulcers, conditions that were not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80 percent of individuals infected with the bacterium are asymptomatic. It has been postulated that it may play an important role in the natural stomach ecology. More than 50% of the world's population harbor H. pylori in their upper gastrointestinal tract. Infection is more prevalent in developing countries and incidence is decreasing in Western countries. H. pylori's helix shape (from which the generic name is derived) is thought to have evolved to penetrate the mucoid lining of the stomach.

Key Points

- In some organisms, hydrogen is oxidized by a membrane-bound hydrogenase causing proton pumping via electron transfer to various quinones and cytochromes.
- Hydrogen-oxidizing organisms, such as Cupriavidus necator (formerly Ralstonia eutropha), often inhabit oxic-anoxic interfaces in nature to take advantage of the hydrogen produced by anaerobic fermentative organisms while still maintaining a supply of oxygen.
- Helicobacter pylori is a Gram-negative, microaerophilic bacterium found in the stomach. It has been postulated that it may play an important role in the natural stomach ecology.

Key Terms

- **Knallgas-bacteria**: Bacteria which oxidize hydrogen.
- **calvin cycle**: A series of biochemical reactions that take place in the stroma of chloroplasts in photosynthetic organisms.

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5.10C: Oxidation of Reduced Sulfur Compounds

Sulfur oxidation involves the oxidation of reduced sulfur compounds, inorganic sulfur, and thiosulfate to form sulfuric acid.

Learning Objectives

- Describe the process of sulfur oxidation

Key Points

- The oxidation of sulfide occurs in stages, with inorganic sulfur being stored either inside or outside of the cell until needed.
- This two step process occurs because sulfide is a better electron donor than inorganic sulfur or thiosulfate; this allows a greater number of protons to be translocated across the membrane.
- Sulfur-oxidizing organisms generate reducing power for carbon dioxide fixation via the Calvin cycle using reverse electron flow—an energy-requiring process that pushes the electrons against their thermodynamic gradient to produce NADH.

Key Terms

- **calvin cycle**: A series of biochemical reactions that take place in the stroma of chloroplasts in photosynthetic organisms.
- **thiosulfate**: Any salt or ester of thiosulfuric acid.
- **chemolithoautotrophic**: The characteristic of a microorganism that obtains energy from the oxidation of inorganic compounds and carbon from the fixation of carbon dioxide.

Sulfur is an essential element for all life, and it is widely used in biochemical processes. In metabolic reactions, sulfur compounds serve as both fuels and respiratory (oxygen-alternative) materials for simple organisms. Sulfur is an important part of many enzymes and antioxidant molecules such as glutathione and thioredoxin.

Sulfur Oxidation

Sulfur oxidation involves the oxidation of reduced sulfur compounds such as sulfide (H_2S), inorganic sulfur (S_0), and thiosulfate ($S_2O_2^{-3}$) to form sulfuric acid (H_2SO_4). An example of a sulfur-oxidizing bacterium is Paracoccus.

Generally, the oxidation of sulfide occurs in stages, with inorganic sulfur being stored either inside or outside of the cell until needed. The two step process occurs because sulfide is a better electron donor than inorganic sulfur or thiosulfate; this allows a greater number of protons to be translocated across the membrane. Sulfur-oxidizing organisms generate reducing power for carbon dioxide fixation via the Calvin cycle using reverse electron flow—an energy-requiring process that pushes the electrons against their thermodynamic gradient to produce NADH. Biochemically, reduced sulfur compounds are converted to sulfite (SO_2^{-3}) and, subsequently, sulfate (SO_2^{-4}) by the enzyme sulfite oxidase. Some organisms, however, accomplish the same oxidation using a reversal of the APS reductase system used by sulfate-reducing bacteria (see above). In all cases the energy liberated is transferred to the electron transport chain for ATP and NADH production. In addition to aerobic sulfur oxidation, some organisms (e.g. Thiobacillus denitrificans) use nitrate (NO^{-3}) as a terminal electron acceptor and therefore grow anaerobically.

Beggiatoa

A classic example of a sulfur-oxidizing bacterium is Beggiatoa, a microbe originally described by Sergei Winogradsky, one of the founders of environmental microbiology. Beggiatoa can be found in marine or freshwater environments. They can usually be found in habitats that have high levels of hydrogen sulfide. These environments include cold seeps, sulfur springs, sewage contaminated water, mud layers of lakes, and near deep hydrothermal vents. Beggiatoa can also be found in the rhizosphere of swamp plants. During his research in Anton de Bary's laboratory of botany in 1887, Russian botanist Winogradsky found that Beggiatoa oxidized hydrogen sulfide (H_2S) as an energy source, forming intracellular sulfur droplets. Winogradsky referred to this form of metabolism as inorgoxidation (oxidation of inorganic compounds). The finding represented the first discovery of lithotrophy.

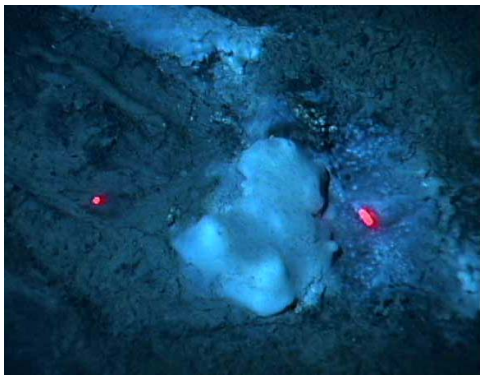

Figure: **A Beggiatoa bacterial mat at the Blake Ridge**: Beggiatoa spp. bacterial mat at a seep on Blake Ridge, off the coast of South Carolina. The red dots are range-finding laser beams. Beggiatoa are able to detoxify hydrogen sulfide in soil.

Beggiatoa can grow chemoorgano-heterotrophically by oxidizing organic compounds to carbon dioxide in the presence of oxygen, though high concentrations of oxygen can be a limiting factor. Organic compounds are also the carbon source for biosynthesis. Some species may oxidize hydrogen sulfide to elemental sulfur as a supplemental source of energy (facultatively litho-heterotroph). This sulfur is stored intracellularly. Some species have the ability of chemolithoautotrophic growth, using sulfide oxidation for energy and carbon dioxide as a source of carbon for biosynthesis. In this metabolic process, internal stored nitrate is the electron acceptor and reduced to ammonia.

Sulfide oxidation: $2H_2S + O_2 \rightarrow 2S + 2H_2O$

Marine autotrophic Beggiatoa species are able to oxidize intracellular sulfur to sulfate. The reduction of elemental sulfur frequently occurs when oxygen is lacking. Sulfur is reduced to sulfide at the cost of stored carbon or by added hydrogen gas. This may be a survival strategy to bridge periods without oxygen

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5.10D: Iron Oxidation

Learning Objectives

- Outline the purpose of iron oxidation and the three types of ferrous iron-oxidizing microbes (acidophiles, microaerophiles and anaerobic photosynthetic bacteria)

Ferric iron (Fe^{3+}) is a widespread anaerobic terminal electron acceptor both for autotrophic and heterotrophic organisms. Electron flow in these organisms is similar to those in electron transport, ending in oxygen or nitrate, except that in ferric iron-reducing organisms the final enzyme in this system is a ferric iron reductase. Model organisms include *Shewanella putrefaciens* and *Geobacter metallireducens*. Since some ferric iron-reducing bacteria (e.g. G. metallireducens) can use toxic hydrocarbons such as toluene as a carbon source, there is significant interest in using these organisms as bioremediation agents in ferric iron-rich contaminated aquifers.



Figure: ***Iron Bacteria****: Common effects of excess iron in water are a reddish-brown color and stained laundry. Iron bacteria are a natural part of the environment in most parts of the world. These microorganisms combine dissolved iron or manganese with oxygen and use it to form rust-colored deposits. In the process, the bacteria produce a brown slime that builds up on well screens, pipes, and plumbing fixtures. Bacteria known to feed on iron are Thiobacillus ferrooxidans and Leptospirillum ferrooxidans.*

Ferrous iron is a soluble form of iron that is stable at extremely low pHs or under anaerobic conditions. Under aerobic, moderate pH conditions ferrous iron is oxidized spontaneously to the ferric (Fe^{3+}) form and is hydrolyzed abiotically to insoluble ferric hydroxide ($Fe(OH)_3$). There are three distinct types of ferrous iron-oxidizing microbes. The first are acidophiles, such as the bacteria Acidithiobacillus ferrooxidans and Leptospirillum ferrooxidans, as well as the archaeon Ferroplasma. These microbes oxidize iron in environments that have a very low pH and are important in acid mine drainage. The second type of microbes oxidizes ferrous iron at cirum-neutral pH. These micro-organisms (for example Gallionella ferruginea or Leptothrix ochracea) live at the oxic-anoxic interfaces and are microaerophiles. The third type of iron-oxidizing microbes is anaerobic photosynthetic bacteria such as Rhodopseudomonas, which use ferrous iron to produce NADH for autotrophic carbon dioxide fixation. Biochemically, aerobic iron oxidation is a very energetically poor process which therefore requires large amounts of iron to be oxidized by the enzyme rusticyanin to facilitate the formation of proton motive force. Like sulfur oxidation, reverse electron flow must be used to form the NADH used for carbon dioxide fixation via the Calvin cycle.

Although ferric iron is the most prevalent inorganic electron acceptor, a number of organisms (including the iron-reducing bacteria mentioned above) can use other inorganic ions in anaerobic respiration. While these processes may often be less significant ecologically, they are of considerable interest for bioremediation, especially when heavy metals or radionuclides are used as electron acceptors. Examples include:

- Manganic ion (Mn^{4+}) reduction to manganous ion]] (Mn^{2+})
- Selenate (SeO_2^{-4}) reduction to selenite (SeO_2^{-3}) and selenite reduction to inorganic selenium (Se_0)
- Arsenate (AsO_3^{-4}) reduction to arsenite (AsO_3^{-3})
- Uranyl ion ion (UO_2^{+2}) reduction to uranium dioxide (UO_2)

Key Points

- Ferrous iron is a soluble form of iron that is stable at extremely low pHs or under anaerobic conditions. Under aerobic, moderate pH conditions ferrous iron is oxidized spontaneously to the ferric (Fe3+) form and is hydrolyzed abiotically to insoluble ferric hydroxide (Fe(OH)3).

- Three distinct types of ferrous iron-oxidizing microbes: acidophiles, microaerophiles that oxidize ferrous iron at cirum-neutral pH, anaerobic photosynthetic bacteria which use ferrous iron to produce NADH for autotrophic carbon dioxide fixation.
- Although ferric iron is the most prevalent inorganic electron acceptor, a number of organisms can use other inorganic ions in anaerobic respiration.

Key Terms

- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **heterotroph**: An organism that requires an external supply of energy in the form of food as it cannot synthesize its own.

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5.10E: Nitrification

Learning Objectives

- Describe the process of nitrification and its importance

Nitrification is the process by which ammonia (NH_3) or ammonium ($NH4^+$) is converted to nitrate (NO_3^-). Nitrification is the net result of two distinct processes: oxidation of ammonium to nitrite (NO_2^-) by nitrosifying or ammonia-oxidizing bacteria and oxidation of nitrite (NO_2^-) to nitrate (NO_3^-) by the nitrite-oxidizing bacteria. Nitrification is an important step in the nitrogen cycle in soil. Nitrification is an aerobic process performed by small groups of autotrophic bacteria and archaea.

Chemistry of Nitrogen Compound Oxidation

Nitrification is a process of nitrogen compound oxidation (effectively, loss of electrons from the nitrogen atom to the oxygen atoms):

1. $2\ NH_4^+ + 3\ O_2 \rightarrow 2\ NO_2^- + 2\ H_2O + 4\ H^+$ (Nitrosomonas)
2. $2\ NO_2^- + O_2 \rightarrow 2\ NO_3^-$ (Nitrobacter, Nitrospina)
3. $NH_3 + O_2 \rightarrow NO_2^- + 3H^+ + 2e^-$
4. $NO_2^- + H_2O \rightarrow NO_3^- + 2H^+ + 2e^-$

Both of these processes are extremely energetically poor, which leads to very slow growth rates for both types of organisms.

Ammonium Oxidation

The transformation of ammonia to nitrite is usually the rate limiting step of nitrification. Biochemically, ammonium oxidation occurs by the stepwise oxidation of ammonium to hydroxylamine (NH_2OH) by the enzyme ammonium monooxygenase in the cytoplasm, followed by the oxidation of hydroxylamine to nitrite by the enzyme hydroxylamine oxidoreductase in the periplasm. Electron and proton cycling are very complex, but as a net result only one proton is translocated across the membrane per molecule of ammonium oxidized.

Nitrite Reduction

Nitrite reduction is much simpler, with nitrite being oxidized by the enzyme nitrite oxidoreductase coupled to proton translocation by a very short electron transport chain, again leading to very low growth rates for these organisms. Oxygen is required in ammonium and nitrite oxidation, meaning that both nitrosifying and nitrite-oxidizing bacteria are aerobes. As in sulfur and iron oxidation, NADH for carbon dioxide fixation using the Calvin cycle is generated by reverse electron flow, thereby placing a further metabolic burden on an already energy-poor process.

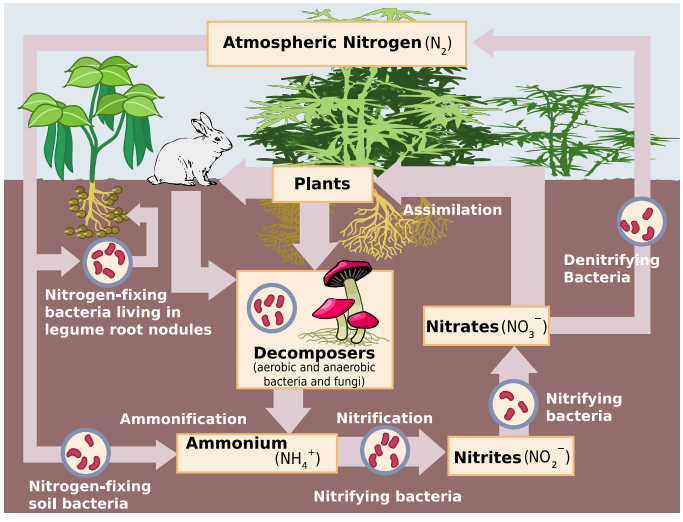

Figure: ***The nitrogen cycle****: Schematic representation of the flow of nitrogen through the environment. The importance of bacteria in the cycle is immediately recognized as being a key element in the cycle, providing different forms of nitrogen compounds assimilable by higher organisms.*

Human Applications of Nitrification

Nitrification is important in agricultural systems, where fertilizer is often applied as ammonia. Nitrification also plays an important role in the removal of nitrogen from municipal wastewater. The conventional removal is nitrification, followed by denitrification.

Key Points

- Nitrification is actually the net result of two distinct processes: the oxidation of ammonia (NH_3) or ammonium (NH_4^+) to nitrite (NO_2^-) by ammonia-oxidizing bacteria (e.g. Nitrosomonas) and the oxidation of nitrite (NO_2^-) to nitrate (NO_3^-) by the nitrite-oxidizing bacteria (e.g. Nitrobacter).
- Nitrification is extremely energetically poor leading to very slow growth rates for both types of organisms.
- Oxygen is required in ammonium and nitrite oxidation; ammonia-oxidizing and nitrite-oxidizing bacteria are aerobes.

Key Terms

- **chemolithotrophy**: A type of metabolism where energy is obtained from the oxidation of inorganic compounds.
- **nitrification**: The biological oxidation of ammonia or ammonium with oxygen into nitrite followed by the oxidation of these nitrites into nitrates.

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5.10F: Anammox

Anammox, an abbreviation for ANaerobic AMMonium OXidation, is a globally significant microbial process of the nitrogen cycle.

Learning Objectives

- Describe the overall process of ANaerobic AMMonium OXidation (Anammox) and its purpose

Key Points

- The bacteria mediating this process were identified in 1999, and at the time were a great surprise for the scientific community.
- This form of metabolism occurs in members of the Planctomycetes (e.g. Candidatus Brocadia anammoxidans) and involves the coupling of ammonia oxidation to nitrite reduction.
- To deal with the high toxicity of hydrazine, anammox bacteria contain a hydrazine-containing intracellular organelle called the anammoxasome, surrounded by highly compact ladderane lipid membrane. These lipids are unique in nature, as is the use of hydrazine as a metabolic intermediate.

Key Terms

- **Anammox**: An abbreviation for ANaerobic AMMonium OXidation, a globally significant microbial process of the nitrogen cycle.
- **anaerobes**: Organisms that do not require oxygen for growth.
- **ladderane**: Any of a class of polycyclic hydrocarbons, consisting of repeating cyclobutane moieties, that resemble ladders

Anammox, an abbreviation for ANaerobic AMMonium OXidation, is a globally significant microbial process of the nitrogen cycle. The bacteria mediating this process were identified in 1999, and at the time were a great surprise to the scientific community. Anammox takes place in many natural environments, contributing up to 50% of the dinitrogen gas produced in the oceans. In this biological process, nitrite and ammonium are converted directly into dinitrogen gas. The overall catabolic reaction is:



Figure: **Enrichment Culture of Anammox Bacterium (Radboud University, Nijmegen)**: Enrichment culture of the anammox bacterium, Kuenenia stuttgartiensis.

$NH_4^+ + NO_2^- \rightarrow N_2 + 2H_2O$.

This form of metabolism involves the coupling of ammonia oxidation to nitrite reduction. Since oxygen is not required for the process, these organisms are strict anaerobes. Amazingly, hydrazine (N_2H_4 — rocket fuel) is produced as an intermediate during anammox metabolism. To deal with the high toxicity of hydrazine, anammox bacteria have a hydrazine-containing intracellular organelle called the anammoxasome (a compartment inside the cytoplasm which is the locus of anammox catabolism), which is surrounded by an unusual and highly compact ladderane lipid membrane. Further, the membranes of these bacteria mainly consist of ladderane lipids so far unique in biology. Of special interest is the conversion to hydrazine (normally used as a high-energy rocket fuel, and poisonous to most living organisms) as an intermediate. A final striking feature of the organism is the extremely slow growth rate. The doubling time is nearly two weeks. The anammox process was originally found to occur only from 20°C to 43°C but more recently, anammox has been observed at temperatures from 36°C to 52°C in hot springs and 60°C to 85°C at hydrothermal vents located along the Mid-Atlantic Ridge.

Anammox organisms are autotrophs although the mechanism for carbon dioxide fixation is still unclear. Because of this property, these organisms could be used industrially to remove nitrogen in wastewater treatment processes. The bacteria that perform the anammox process belong to the bacterial phylum Planctomycetes (e.g. Candidatus Brocadia anammoxidans), of which Planctomyces and Pirellula are the best known genera. Currently five genera of anammox bacteria have been (provisionally) defined: Brocadia, Kuenenia, Anammoxoglobus, Jettenia (all fresh water species), and Scalindua (marine species).

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5.10G: Benzoate Catabolism

Rhodobacter sphaeroides is able to produce hydrogen from a wide range of organic compounds (chiefly organic acids) and light.

Learning Objectives

- List a function of Rhodococcus in the scientific community

Key Points

- In the absence of water-splitting, photosynthesis is anoxygenic. Therefore, hydrogen production is sustained without inhibition from generated oxygen.
- Strains of Rhodococcus are applicably important owing to their ability to catabolize a wide range of compounds and produce bioactive steroids, acrylamide, and acrylic acid, and their involvement in fossil fuel biodesulfurization.
- The use of Rhodococcus is borne out of its ability to metabolize harmful environmental pollutants, such as toluene, naphthalene, herbicides, and PCBs.

Key Terms

- **catabolism**: Destructive metabolism, usually includes the release of energy and breakdown of materials.
- **Rhodococcus**: a genus of aerobic, nonsporulating, nonmotile Gram-positive bacteria closely related to Mycobacteria and Corynebacteria.
- **benzoate**: Any salt or ester of benzoic acid.

Benzoate catabolism is a series of chemical reactions resulting in the breakdown of benzoate. The purple non-sulphur (PNS) bacteria Rhodobacter sphaeroides is able to produce hydrogen from a wide range of organic compounds (chiefly organic acids) and light. The photo-system required for hydrogen production in Rhodobacter (PS-I) differ from its oxygenic photosystem (PS-II) due to the requirement of organic acids and the inability to oxidize water. In the absence of water-splitting, photosynthesis is anoxygenic. Therefore, hydrogen production is sustained without inhibition from generated oxygen. In PNS bacteria, hydrogen production is due to catalysis by nitrogenase. Hydrogenases are also present but the production of hydrogen by [FeFe]-hydrogenase is less than ten times the hydrogen uptake by [NiFe]-hydrogenase. Only under nitrogen-deficient conditions is nitrogenase activity sufficient to overcome uptake hydrogenase activity, resulting in net generation of hydrogen.

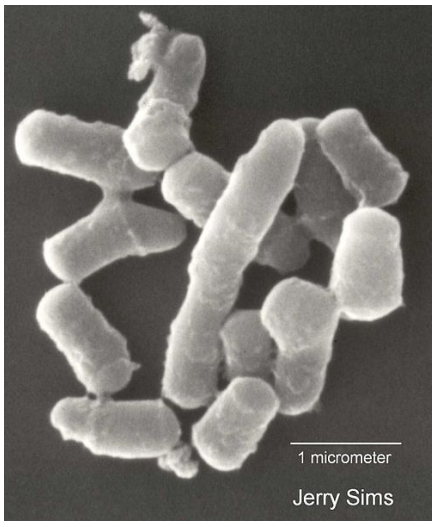

Figure: **Scanning electron micrograph of Rhodococcus sp. strain Q1**: Rhodococcus sp. strain Q1 grown on quinoline – the organism can use quinoline as a sole source of carbon, nitrogen and energy, tolerating concentrations up to 3.88 millimoles per liter.

Rhodococcus is a genus of aerobic, nonsporulating, nonmotile Gram-positive bacteria closely related to Mycobacteria and Corynebacteria. While a few species are pathogenic, most are benign and have been found to thrive in a broad range of environments, including soil, water, and eukaryotic cells. Fully sequenced in October 2006, the genome is known to be 9.7 megabasepairs long and 67% G/C. Strains of Rhodococcus are applicably important owing to their ability to catabolize a wide range of compounds and produce bioactive steroids, acrylamide, and acrylic acid, and their involvement in fossil fuel biodesulfurization. This genetic and catabolic diversity is not only due to the large bacterial chromosome, but also to the presence

of three large linear plasmids. Rhodococcus is also an experimentally advantageous system owing to a relatively fast growth rate and simple developmental cycle. However, as it stands now, Rhodococcus is not well characterized. Another important application of Rhodococcus comes from bioconversion, using biological systems to convert cheap starting material into more valuable compounds. This use of Rhodococcus is borne out of its ability to metabolize harmful environmental pollutants, such as toluene, naphthalene, herbicides, and PCBs. Rhodococci typically metabolize aromatic substrates by first oxygenating the aromatic ring to form a diol (two alcohol groups). Then, the ring is cleaved with intra/extradiol mechanisms, opening the ring and exposing the substrate to further metabolism. Since the chemistry here is very stereospecific, the diols are created with predictable chirality. While controlling the chirality of chemical reaction presents a significant challenge for synthetic chemists, biological processes can be used instead to faithfully produce chiral molecules in cases where direct chemical synthesis is infeasible or inefficient. An example of this is the use of Rhodococcus to produce indene, a precursor to the AIDS drug Crixivan^{TM}, a protease inhibitor, and containing two of the five chiral centers needed in the complex.

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5.10H: Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons are potent atmospheric pollutants that consist of fused aromatic rings and do not contain heteroatoms.

Learning Objectives

- Recognize various sources of polycyclic aromatic hydrocarbons and means of removal (bio-, phy

Key Points

- Polycyclic aromatic hydrocarbons (PAHs) occur in oil, coal, and tar deposits, and they are produced as byproducts of fuel burning (whether fossil fuel or biomass).
- Bioremediation is the use of microorganism metabolism to remove pollutants. These technologies can be generally classified as *in situ* or *ex situ*.
- Mycoremediation is a form of bioremediation that uses fungi to degrade or sequester contaminants in the environment. Stimulating microbial and enzyme activity, mycelium reduces toxins *in situ*.

Key Terms

- **Polycyclic aromatic hydrocarbons**: also known as poly-aromatic hydrocarbons or polynuclear aromatic hydrocarbons, are potent atmospheric pollutants that consist of fused aromatic rings and do not contain heteroatoms or carry substituents.
- **carcinogenic**: Causing or tending to cause cancer.
- **mutagenic**: Capable of causing mutation.

PAHs

Polycyclic aromatic hydrocarbons (PAHs), also known as poly-aromatic hydrocarbons or polynuclear aromatic hydrocarbons, are seen in. PAHs are potent atmospheric pollutants that consist of fused aromatic rings and do not contain heteroatoms or carry substituents. Naphthalene is the simplest example of a PAH. PAHs occur in oil, coal, and tar deposits, and are produced as byproducts of fuel burning (whether fossil fuel or biomass). As a pollutant, they are of concern because some compounds have been identified as carcinogenic, mutagenic, and teratogenic. PAHs are also found in cooked foods—studies have found PAHs in meat cooked at high temperatures such as grilling or barbecuing, and in smoked fish. They are also found in the interstellar medium, comets, and meteorites. PAHs are a candidate for the molecule acted as a basis for the earliest forms of life. In graphene the PAH motif is extended to large 2D sheets.

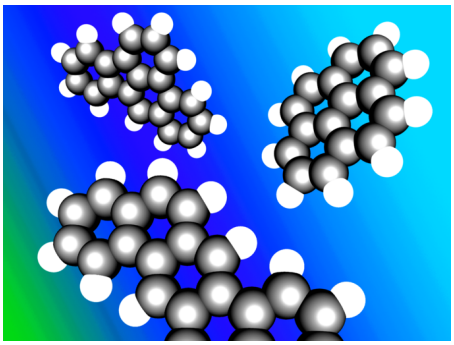

Figure: **Polycyclic Aromatic Hydrocarbons**: An image showing three examples of polycyclic aromatic hydrocarbons. Clockwise from top left, the molecules are: benz[e]acephenanthrylene, pyrene and dibenz[a,h]anthracene.

Natural crude oil and coal deposits contain significant amounts of PAHs from chemical conversion of natural product molecules, such as steroids, to aromatic hydrocarbons. They are also found in processed fossil fuels, tar, and various edible oils.

PLFA Analysis

Phospholipid -derived fatty acids (PLFA) are widely used in microbial ecology as chemotaxonomic markers of bacteria and other organisms. Phospholipids are the primary lipids composing cellular membranes. They can be esterified to many types of fatty acids. Once the phospholipids of an unknown sample are esterfied, the composition of the resulting PLFA can be compared to the

PLFA of known organisms to determine the identity of the sample organism. PLFA analysis may be combined with stable isotope probing to determine which microbes are metabolically active in a sample.

The basic premise for PLFA analysis is that as individual organisms (especially bacteria and fungi) die, phospholipids are rapidly degraded and the remaining phospholipid content of the sample is assumed to be from living organisms. As the phospholipids of different groups of bacteria and fungi contain a variety of somewhat unique fatty acids, they can serve as useful biomarkers for such groups. PLFA profiles and composition can be determined by purifying the phospholipids and then cleaving the fatty acids for further analysis.

Bioremediation

Bioremediation is the use of micro-organism metabolism to remove pollutants. Technologies can be generally classified as *in situ* or *ex situ*. *In situ*bioremediation involves treating the contaminated material at the site, while *ex situ* involves the removal of the contaminated material to be treated elsewhere. Some examples of bioremediation related technologies are phytoremediation, bioventing, bioleaching, landfarming, bioreactor, composting, bioaugmentation, rhizofiltration, and biostimulation.

Bioremediation can occur on its own (natural attenuation or intrinsic bioremediation) or can be spurred on via the addition of fertilizers to increase the bioavailability within the medium (biostimulation). Recent advancements have found success by adding matched microbe strains to the medium to enhance the resident microbe population ‘s ability to break down contaminants. Microorganisms used to perform the function of bioremediation are known as bioremediators. Not all contaminants, however, are easily treated by bioremediation using microorganisms. For example, heavy metals such as cadmium and lead are not readily absorbed or captured by microorganisms. The assimilation of metals such as mercury into the food chain may worsen matters.

Phytoremediation

Phytoremediation is useful in these circumstances because natural plants or transgenic plants are able to bioaccumulate these toxins in their above-ground parts, which are then harvested for removal. The heavy metals in the harvested biomass may be further concentrated by incineration or recycled for industrial use. The elimination of a wide range of pollutants and wastes from the environment requires increasing our understanding of the relative importance of different pathways and regulatory networks to carbon flux in particular environments and for particular compounds, and they will certainly accelerate the development of bioremediation technologies and biotransformation processes.

Mycoremediation

Mycoremediation, is a form of bioremediation, the process of using fungi to degrade or sequester contaminants in the environment. Stimulating microbial and enzyme activity, mycelium reduces toxins *in situ*. Some fungi are hyperaccumulators, capable of absorbing and concentrating heavy metals in the mushroom fruit bodies. One of the primary roles of fungi in the ecosystem is decomposition, which is performed by the mycelium. The mycelium secretes extracellular enzymes and acids that break down lignin and cellulose, the two main building blocks of plant fiber. These organic compounds are composed of long chains of carbon and hydrogen, structurally similar to many organic pollutants. The key to mycoremediation is determining the right fungal species to target a specific pollutant.

Gallaecimonas is a recently described genus of bacteria. It is a Gram-negative, rod-shaped, halotolerant bacterium in the class Gammaproteobacteria. It can degrade high molecular mass polycyclic aromatic hydrocarbons of 4 and 5 rings. The 16S rRNA gene sequences of the type strain CEE_131(T) proved to be distantly related to those of Rheinheimera and Serratia.

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SECTION OVERVIEW

5.11: Phototrophy

Topic hierarchy

5.11A: The Purpose and Process of Photosynthesis

5.11B: Main Structures and Summary of Photosynthesis

5.11C: The Two Parts of Photosynthesis

5.11D: Bacteriorhodopsin

5.11E: Carotenoids and Phycobilins

5.11F: Facultative Phototrophy

5.11G: Oxygenic Photosynthesis

5.11H: Anoxygenic Photosynthesis

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5.11A: The Purpose and Process of Photosynthesis

The process of photosynthesis converts light energy to chemical energy, which can be used by organisms for different metabolic processes.

Learning Objectives

- Describe the process of photosynthesis

Key Points

- Photosynthesis evolved as a way to store the energy in solar radiation as high-energy electrons in carbohydrate molecules.
- Plants, algae, and cyanobacteria, known as photoautotrophs, are the only organisms capable of performing photosynthesis.
- Heterotrophs, unable to produce their own food, rely on the carbohydrates produced by photosynthetic organisms for their energy needs.

Key Terms

- **photosynthesis**: the process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts
- **photoautotroph**: an organism that can synthesize its own food by using light as a source of energy
- **chemoautotroph**: a simple organism, such as a protozoan, that derives its energy from chemical processes rather than photosynthesis

The Importance of Photosynthesis

The processes of all organisms—from bacteria to humans—require energy. To get this energy, many organisms access stored energy by eating food. Carnivores eat other animals and herbivores eat plants. But where does the stored energy in food originate? All of this energy can be traced back to the process of photosynthesis and light energy from the sun.

Photosynthesis is essential to all life on earth. It is the only biological process that captures energy from outer space (sunlight) and converts it into chemical energy in the form of G3P (
Glyceraldehyde 3-phosphate) which in turn can be made into sugars and other molecular compounds. Plants use these compounds in all of their metabolic processes; plants do not need to consume other organisms for food because they build all the molecules they need. Unlike plants, animals need to consume other organisms to consume the molecules they need for their metabolic processes.

The Process of Photosynthesis

During photosynthesis, molecules in leaves capture sunlight and energize electrons, which are then stored in the covalent bonds of carbohydrate molecules. That energy within those covalent bonds will be released when they are broken during cell respiration. How long lasting and stable are those covalent bonds? The energy extracted today by the burning of coal and petroleum products represents sunlight energy captured and stored by photosynthesis almost 200 million years ago.

Plants, algae, and a group of bacteria called cyanobacteria are the only organisms capable of performing photosynthesis. Because they use light to manufacture their own food, they are called photoautotrophs (“self-feeders using light”). Other organisms, such as animals, fungi, and most other bacteria, are termed heterotrophs (“other feeders”) because they must rely on the sugars produced by photosynthetic organisms for their energy needs. A third very interesting group of bacteria synthesize sugars, not by using sunlight’s energy, but by extracting energy from inorganic chemical compounds; hence, they are referred to as chemoautotrophs.

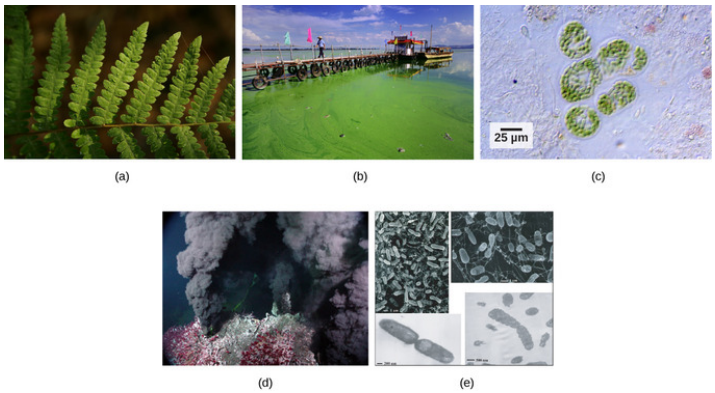

Figure: **Photosynthetic and Chemosynthetic Organisms**: Photoautotrophs, including (a) plants, (b) algae, and (c) cyanobacteria, synthesize their organic compounds via photosynthesis using sunlight as an energy source. Cyanobacteria and planktonic algae can grow over enormous areas in water, at times completely covering the surface. In a (d) deep sea vent, chemoautotrophs, such as these (e) thermophilic bacteria, capture energy from inorganic compounds to produce organic compounds. The ecosystem surrounding the vents has a diverse array of animals, such as tubeworms, crustaceans, and octopi that derive energy from the bacteria.

The importance of photosynthesis is not just that it can capture sunlight's energy. A lizard sunning itself on a cold day can use the sun's energy to warm up. Photosynthesis is vital because it evolved as a way to store the energy in solar radiation (the "photo-" part) as high-energy electrons in the carbon-carbon bonds of carbohydrate molecules (the "-synthesis" part). Those carbohydrates are the energy source that heterotrophs use to power the synthesis of ATP via respiration. Therefore, photosynthesis powers 99 percent of Earth's ecosystems. When a top predator, such as a wolf, preys on a deer, the wolf is at the end of an energy path that went from nuclear reactions on the surface of the sun, to light, to photosynthesis, to vegetation, to deer, and finally to wolf.

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5.11B: Main Structures and Summary of Photosynthesis

In multicellular autotrophs, the main cellular structures that allow photosynthesis to take place include chloroplasts, thylakoids, and chlorophyll.

Learning Objectives

- Describe the main structures involved in photosynthesis and recall the chemical equation that summarizes the process of photosynthesis

Key Points

- The chemical equation for photosynthesis is $6CO2+6H2O \rightarrow C6H12O6+6O2$.$6CO2+6H2O \rightarrow C6H12O6+6O2$.
- In plants, the process of photosynthesis takes place in the mesophyll of the leaves, inside the chloroplasts.
- Chloroplasts contain disc-shaped structures called thylakoids, which contain the pigment chlorophyll.
- Chlorophyll absorbs certain portions of the visible spectrum and captures energy from sunlight.

Key Terms

- **chloroplast**: An organelle found in the cells of green plants and photosynthetic algae where photosynthesis takes place.
- **mesophyll**: A layer of cells that comprises most of the interior of the leaf between the upper and lower layers of epidermis.
- **stoma**: A pore in the leaf and stem epidermis that is used for gaseous exchange.

Overview of Photosynthesis

Photosynthesis is a multi-step process that requires sunlight, carbon dioxide, and water as substrates. It produces oxygen and glyceraldehyde-3-phosphate (G3P or GA3P), simple carbohydrate molecules that are high in energy and can subsequently be converted into glucose, sucrose, or other sugar molecules. These sugar molecules contain covalent bonds that store energy. Organisms break down these molecules to release energy for use in cellular work.

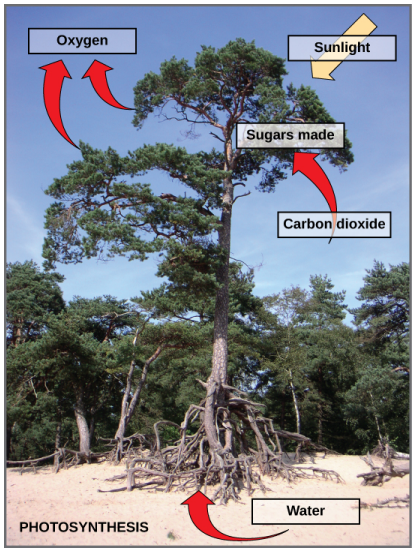

Figure: **Photosynthesis**: Photosynthesis uses solar energy, carbon dioxide, and water to produce energy-storing carbohydrates. Oxygen is generated as a waste product of photosynthesis.

The energy from sunlight drives the reaction of carbon dioxide and water molecules to produce sugar and oxygen, as seen in the chemical equation for photosynthesis. Though the equation looks simple, it is carried out through many complex steps. Before learning the details of how photoautotrophs convert light energy into chemical energy, it is important to become familiar with the structures involved.

Photosynthesis Equation						
Carbon dioxide	+	Water	SUNLIGHT →	Sugar	+	Oxygen
$6CO_2$		$6H_2O$		$C_6H_{12}O_6$		$6O_2$

Figure: **Chemical equation for photosynthesis**: The basic equation for photosynthesis is deceptively simple. In reality, the process includes many steps involving intermediate reactants and products. Glucose, the primary energy source in cells, is made from two three-carbon GA3P molecules.

Photosynthesis and the Leaf

In plants, photosynthesis generally takes place in leaves, which consist of several layers of cells. The process of photosynthesis occurs in a middle layer called the mesophyll. The gas exchange of carbon dioxide and oxygen occurs through small, regulated openings called stomata (singular: stoma), which also play a role in the plant's regulation of water balance. The stomata are typically located on the underside of the leaf, which minimizes water loss. Each stoma is flanked by guard cells that regulate the opening and closing of the stomata by swelling or shrinking in response to osmotic changes.

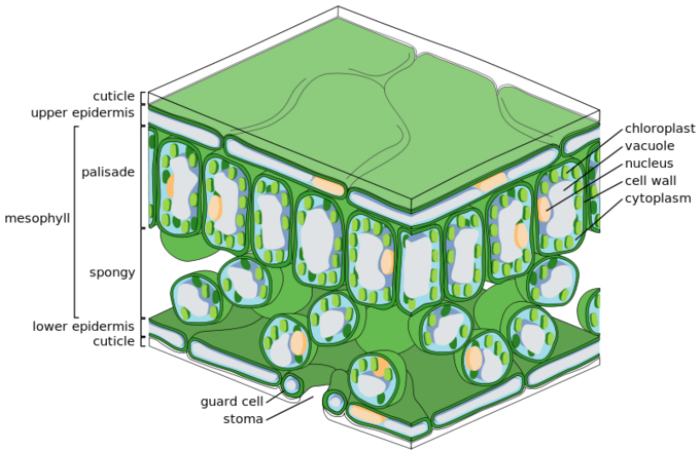

Figure: **Structure of a leaf (cross-section)**: Photosynthesis takes place in the mesophyll. The palisade layer contains most of the chloroplast and principal region in which photosynthesis is carried out. The airy spongy layer is the region of storage and gas exchange. The stomata regulate carbon dioxide and water balance.

Photosynthesis within the Chloroplast

In all autotrophic eukaryotes, photosynthesis takes place inside an organelle called a chloroplast. For plants, chloroplast-containing cells exist in the mesophyll. Chloroplasts have a double membrane envelope composed of an outer membrane and an inner membrane. Within the double membrane are stacked, disc-shaped structures called thylakoids.

Embedded in the thylakoid membrane is chlorophyll, a pigment that absorbs certain portions of the visible spectrum and captures energy from sunlight. Chlorophyll gives plants their green color and is responsible for the initial interaction between light and plant material, as well as numerous proteins that make up the electron transport chain. The thylakoid membrane encloses an internal space called the thylakoid lumen. A stack of thylakoids is called a granum, and the liquid-filled space surrounding the granum is the stroma or "bed."

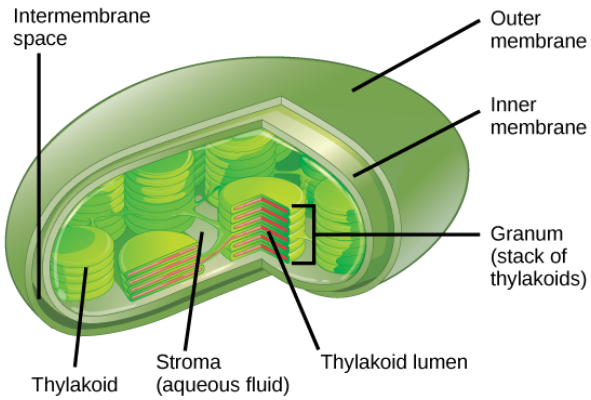

Figure: **Structure of the Chloroplast**: Photosynthesis takes place in chloroplasts, which have an outer membrane and an inner membrane. Stacks of thylakoids called grana form a third membrane layer.

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5.11C: The Two Parts of Photosynthesis

Light-dependent and light-independent reactions are two successive reactions that occur during photosynthesis.

Learning Objectives

- Distinguish between the two parts of photosynthesis

Key Points

- In light-dependent reactions, the energy from sunlight is absorbed by chlorophyll and converted into chemical energy in the form of electron carrier molecules like ATP and NADPH.
- Light energy is harnessed in Photosystems I and II, both of which are present in the thylakoid membranes of chloroplasts.
- In light-independent reactions (the Calvin cycle), carbohydrate molecules are assembled from carbon dioxide using the chemical energy harvested during the light-dependent reactions.

Key Terms

- **photosystem**: Either of two biochemical systems active in chloroplasts that are part of photosynthesis.

Photosynthesis takes place in two sequential stages:

1. The light-dependent reactions;
2. The light-independent reactions, or Calvin Cycle.

Light-Dependent Reactions

Just as the name implies, light-dependent reactions require sunlight. In the light-dependent reactions, energy from sunlight is absorbed by chlorophyll and converted into stored chemical energy, in the form of the electron carrier molecule NADPH (nicotinamide adenine dinucleotide phosphate) and the energy currency molecule ATP (adenosine triphosphate). The light-dependent reactions take place in the thylakoid membranes in the granum (stack of thylakoids), within the chloroplast.

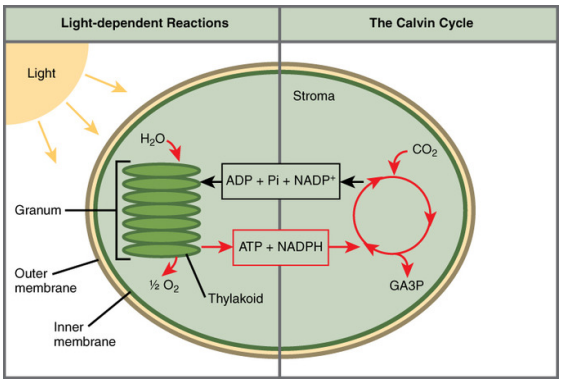

Figure: **The two stages of photosynthesis**: Photosynthesis takes place in two stages: light-dependent reactions and the Calvin cycle (light-independent reactions). Light-dependent reactions, which take place in the thylakoid membrane, use light energy to make ATP and NADPH. The Calvin cycle, which takes place in the stroma, uses energy derived from these compounds to make GA3P from CO2.

Photosystems

The process that converts light energy into chemical energy takes place in a multi-protein complex called a photosystem. Two types of photosystems are embedded in the thylakoid membrane: photosystem II (PSII) and photosystem I (PSI). Each photosystem plays a key role in capturing the energy from sunlight by exciting electrons. These energized electrons are transported by “energy carrier” molecules, which power the light-independent reactions.

Photosystems consist of a light-harvesting complex and a reaction center. Pigments in the light-harvesting complex pass light energy to two special chlorophyll *a* molecules in the reaction center. The light excites an electron from the chlorophyll *a* pair, which passes to the primary electron acceptor. The excited electron must then be replaced. In photosystem II, the electron comes from the splitting of water, which releases oxygen as a waste product. In photosystem I, the electron comes from the chloroplast electron transport chain.

The two photosystems oxidize different sources of the low-energy electron supply, deliver their energized electrons to different places, and respond to different wavelengths of light.

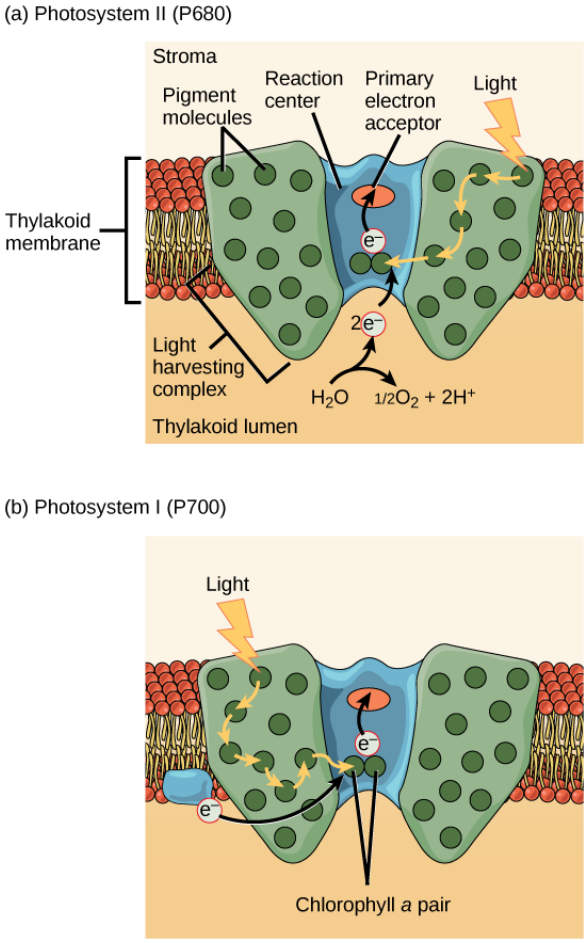

Figure: **Photosystems I & II**: As explained above, the photosystems manipulate electrons with energy harvested from light.

Light-Independent Reactions

In the light-independent reactions or Calvin cycle, the energized electrons from the light-dependent reactions provide the energy to form carbohydrates from carbon dioxide molecules. The light-independent reactions are sometimes called the Calvin cycle because of the cyclical nature of the process.

Although the light-independent reactions do not use light as a reactant (and as a result can take place at day or night), they require the products of the light-dependent reactions to function. The light-independent molecules depend on the energy carrier molecules, ATP and NADPH, to drive the construction of new carbohydrate molecules. After the energy is transferred, the energy carrier molecules return to the light-dependent reactions to obtain more energized electrons. In addition, several enzymes of the light-independent reactions are activated by light.

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5.11D: Bacteriorhodopsin

Bacteriorhodopsin acts a proton pump, generating cellular energy in a manner independent of chlorophyll.

Learning Objectives

- Discuss the function of bacteriorhodopsin

Key Points

- Bacteriorhodopsin is a proton pump found in Archaea, it takes light energy and coverts it into chemical energy, ATP, that can be used by the cell for cellular functions.
- Bacteriorhodopsin forms chains, which contain retinal molecule within, it is the retinal molecule that absorbs a photon from light, it then changes the confirmation of the nearby Bacteriorhodopsin protein, allowing it to act as a proton pump.
- While chlorophyll based ATP generation depends on a protein gradient, like bacteriorhodopsin, but with striking differences, suggesting that phototrophy evolved in bacteria and archaea independently of each other.

Key Terms

- **isomerized**: converted from one isomer to another
- **retinal**: One of several yellow or red carotenoid pigments formed from rhodopsin by the action of light; retinene
- **phototrophy**: The synthesis of an organism's food from inorganic material using light as a source of energy

Bacteriorhodopsin is a protein used by Archaea, the most notable one being Halobacteria. It acts as a proton pump; that is, it captures light energy and uses it to move protons across the membrane out of the cell. The resulting proton gradient is subsequently converted into chemical energy. The resulting proton gradient is subsequently converted into chemical energy.

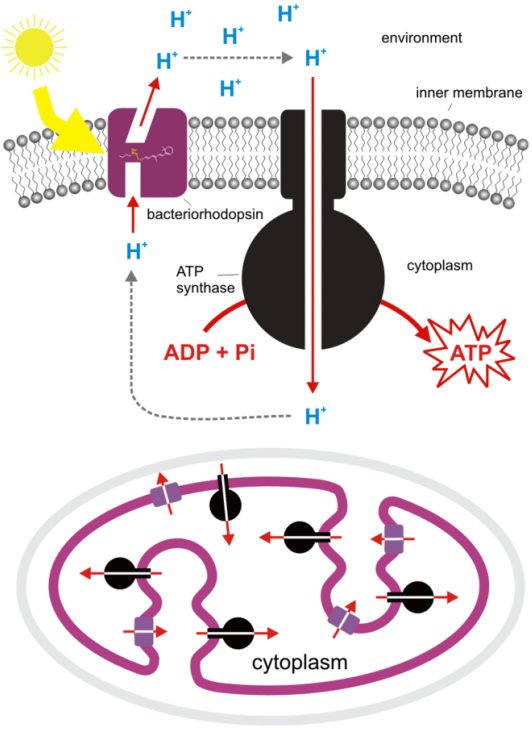

Figure: **ATP generation via bacteriorhodopsin**: Chemiosmotic coupling between sun energy, bacteriorhodopsin and phosphorylation by ATP synthase (chemical energy) during photosynthesis in Halobacterium salinarum (syn. H. halobium).

Bacteriorhodopsin is an integral membrane protein usually found in two-dimensional crystalline patches known as "purple membrane", which can occupy up to nearly 50% of the surface area of the archaeal cell. The bacteriorhodopsin forms repeating elements that are arranged in chains. Each chain has seven transmembrane alpha helices and contains one molecule of retinal buried deep within, the typical structure for retinylidene proteins. It is the retinal molecule that changes its conformation when absorbing a photon, resulting in a conformational change of the surrounding protein and the proton pumping action. This releases a

proton from a “holding site” into the extracellular side (EC) of the membrane. Reprotonation of the retinal molecule by restores its original isomerized form. This results in a second proton being released to the EC side. The releases the proton from its “holding site,” where a new cycle may begin.

The bacteriorhodopsin molecule is purple and is most efficient at absorbing green light (wavelength 500-650 nm, with the absorption maximum at 568 nm). Bacteriorhodopsin belongs to a family of bacterial proteins related to vertebrate rhodopsins, the pigments that sense light in the retina. Many molecules have homology to bacteriorhodopsin, including the light-driven chloride pump halorhodopsin, and some directly light-activated channels like channelrhodopsin. All other phototrophic systems in bacteria, algae, and plants use chlorophylls or bacteriochlorophylls rather than bacteriorhodopsin. These also produce a proton gradient, but in a quite different and more indirect way involving an electron transfer chain consisting of several other proteins. Furthermore, chlorophylls are aided in capturing light energy by other pigments known as “antennas”; these are not present in bacteriorhodopsin-based systems. Last, chlorophyll-based phototrophy is coupled to carbon fixation (the incorporation of carbon dioxide into larger organic molecules) and for that reason is photosynthesis, which is not true for bacteriorhodopsin-based system. Thus, it is likely that phototrophy independently evolved at least twice, once in bacteria and once in archaea.

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5.11E: Carotenoids and Phycobilins

To aid chlorophylls in the absorption of light not many photosynthetic organisms use carotenoids and phycobilins.

Learning Objectives

- Distinguish between carotenoids and phycobilins

Key Points

- Chlorophylls absorb light most efficiently at the ultraviolet end of the spectrum, however not all light that an organism gets is at that wavelength. Thus many photosynthetic organisms rely on accessory compounds to get light from different spectrums.
- Caretenoids aid in the absorption of light in the blue-range spectrum, while at the same time help with the oxidative stress due to the photosynthetic process.
- Phycobilins aid in the absorption of light in the red, orange, yellow, and green light, wavelengths.

Key Terms

- **isoprene**: An unsaturated hydrocarbon, C5H8, that is readily polymerized; natural rubber (caoutchouc) is cis-1,4-polyisoprene, and trans-1,4-polyisoprene is present in gutta-percha and balata; it is the structural basis for the terpenes.
- **photosynthesis**: The process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts.

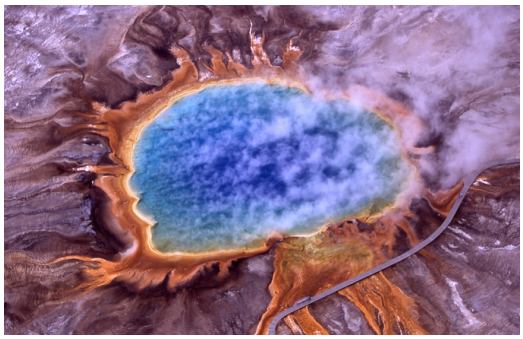

Figure: **Microbial Mats Around the Grand Prismatic Spring**: Thermophiles produce some of the bright colors of Grand Prismatic Spring, Yellowstone National Park. The color of the mats of algae and bacteria is due to the ratio of chlorophyll to carotenoid molecules produced by the organisms. During summertime the chlorophyll content of the organisms is low and thus the mats appear orange, red, or yellow. However during the winter, the mats are usually dark green, because sunlight is more scarce and the microbes produce more chlorophyll to compensate, thereby masking the carotenoid colors.

Photosynthesis in many plants and algae depend on chlorophylls which absorb light closer to the ultraviolet side of the spectrum, and emit light in the green end of the spectrum. However during certain times of the year or in various location most of the light may be shifted to other wavelengths away from the ultraviolet spectrum. To deal with these problems, organisms dependent on photosynthesis express various compounds that allow them to absorb different spectrum of light. Notably are carotenoids and phycobilins.

Chromoplasts of plants and some other photosynthetic organisms like algae, some bacteria, and some fungi. Carotenoids can be produced from fats and other basic organic metabolic building blocks by all these organisms. Carotenoids generally cannot be manufactured by species in the animal kingdom so animals obtain carotenoids in their diets, and may employ them in various ways in metabolism.There are over 600 known carotenoids; they are split into two classes, xanthophylls (which contain oxygen) and carotenes (which are purely hydrocarbons, and contain no oxygen). All carotenoids are tetraterpenoids, meaning that they are produced from 8 isoprene molecules and contain 40 carbon atoms. Carotenoids in general absorb blue light. They serve two key roles in plants and algae: they absorb light energy for use in photosynthesis, and they protect chlorophyll from photodamage.

Phycobilins (from Greek: φ (phykos) meaning “alga”, and from Latin: bilis meaning “bile”) are chromophores (light-capturing molecules) found in cyanobacteria and in the chloroplasts of red algae, glaucophytes and some cryptomonads (though not in green algae and higher plants). They are unique among the photosynthetic pigments in that they are bonded to certain water-soluble proteins, known as phycobiliproteins. Phycobiliproteins then pass the light energy to chlorophylls for photosynthesis.The phycobilins are especially efficient at absorbing red, orange, yellow, and green light, wavelengths that are not well absorbed by

chlorophyll a. Organisms growing in shallow waters tend to contain phycobilins that can capture yellow/red light, while those at greater depth often contain more of the phycobilins that can capture green light, which is relatively more abundant there.

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5.11F: Facultative Phototrophy

A facultative phototroph can rely on photosynthesis and alternative energy sources to survive and grow.

Learning Objectives

- Recognize the traits associated with the classification of facultative phototrophy

Key Points

- Phototrophs can obtain cellular energy from light as well as using light to fix carbon to make complex macromolecules on which to survive.
- Chlamydomonas reinhardtii is an organism that can rely on photosynthetic and chemical energy sources, depending on conditions.
- Facultative means optional, in terms of biology it refers to an organism that can switch energy sources for survival.

Key Terms

- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **pyrenoid**: any of several transparent structures found in the chloroplast of certain algae etc.; they are responsible for the fixation of carbon dioxide and the formation of starch

An autotroph or “producer”, is an organism that produces complex organic compounds (such as carbohydrates, fats, and proteins) from simple substances present in its surroundings, generally using energy from light (photosynthesis) or inorganic chemical reactions (chemosynthesis). They are the producers in a food chain, such as plants on land or algae in water. They are able to make their own food, and do not need a living energy or carbon source. Autotrophs can reduce carbon dioxide to make organic compounds, creating a store of chemical energy. Phototrophs, a type of autotroph, convert physical energy from sunlight (in case of green plants) into chemical energy in the form of reduced carbon.

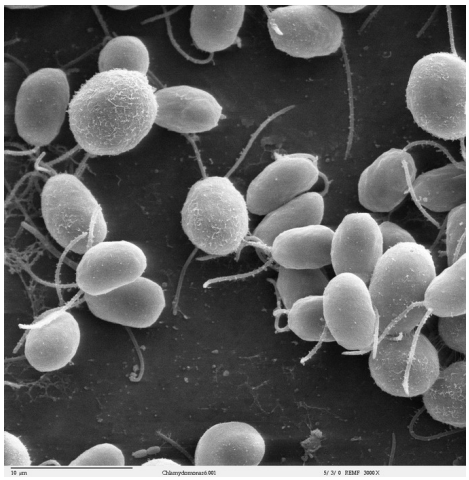

Figure: **Chlamydomanas reinhardtii**: Scanning electron microscope image, showing an example of green algae (Chlorophyta).

In terms of biology facultative means “optional” or “discretionary” the antonym of which is obligate meaning “by necessity”. Thus facultative phototrophy means an organism that can switch between phototrophy to make organix compounds and other means of getting cellular energy. Probably the best studied example of a facultative phototrophy is Chlamydomonas reinhardtii.

Chlamydomonas reinhardtii is a single celled green alga about 10 micrometres in diameter that swims with two flagella. It has a cell wall made of hydroxyproline-rich glycoproteins, a large cup-shaped chloroplast, a large pyrenoid, and an “eyespot” that senses light. Although widely distributed worldwide in soil and fresh water, C. reinhardtii is primarily used as a model organism in biology in a wide range of subfields. When illuminated, C. reinhardtii can grow in media lacking organic carbon and chemical energy sources, and can also grow in the dark when supplied with these. C. reinhardtii is also of interest in the biofuel field, as a source of hydrogen. As one can imagine switching energy sources under varying conditions allows facultative microbes to live in different conditions, in the case of a facultative phototroph it can rely of light other energy sources.

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5.11G: Oxygenic Photosynthesis

Oxygenic photosynthesis, provides energy to organism and allows for carbon fixation, all the while producing oxygen as a byproduct.

Learning Objectives

- Describe oxygenic photosynthesis

Key Points

- Plants, algae and cyanobacteria release oxygen during photosynthesis.
- Photosynthesis is also needed for carbon fixation.
- While different organisms may have differences during oxygenic photosynthesis, they all follow the general equation of, carbon dioxide + water + light energy → carbohydrate + oxygen.

Key Terms

- **cyanobacteria**: Cyanobacteria, also known as blue-green bacteria, blue-green algae, and Cyanophyta, is a phylum of bacteria that obtain their energy through photosynthesis.
- **oxygenic**: of, relating to, containing or producing oxygen

In plants, algae and cyanobacteria, photosynthesis releases oxygen. This is called oxygenic photosynthesis. Although there are some differences between oxygenic photosynthesis in plants, algae, and cyanobacteria, the overall process is quite similar in these organisms. Photosynthesis is not only needed by photosynthetic organism for energy but also for carbon fixation.

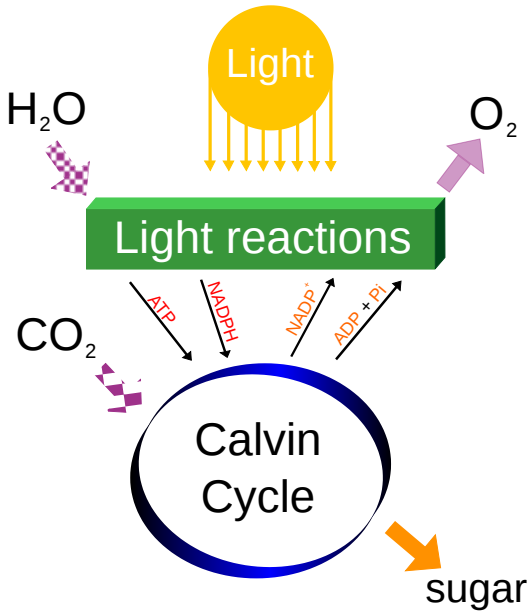

Figure: **Photosynthesis overview**: Photosynthesis changes sunlight into chemical energy, splits water to liberate O2, and fixes CO2 into sugar.

Carbon dioxide is converted into sugars in a process called carbon fixation. Carbon fixation is a redox reaction, so photosynthesis needs to supply both a source of energy to drive this process, and the electrons needed to convert carbon dioxide into a carbohydrate, which is a reduction reaction. In general outline, photosynthesis is the opposite of cellular respiration, where glucose and other compounds are oxidized to produce carbon dioxide, water, and release chemical energy. However, the two processes take place through a different sequence of chemical reactions and in different cellular compartments. The general equation for photosynthesis is therefore:

2n CO2 + 2n DH2 + photons → $2(CH_2O)n$ + 2n DO

Carbon dioxide + electron donor + light energy → carbohydrate + oxidized electron donor.

In oxygenic photosynthesis water is the electron donor and, since its hydrolysis releases oxygen, the equation for this process is:

$2n\ CO_2 + 4n\ H_2O + photons \rightarrow 2(CH_2O)n + 2n\ O_2 + 2n\ H_2O$

carbon dioxide + water + light energy → carbohydrate + oxygen + water

Often 2n water molecules are cancelled on both sides, yielding:

$2n\ CO_2 + 2n\ H_2O + photons \rightarrow 2(CH_2O)n + 2n\ O_2$

carbon dioxide + water + light energy → carbohydrate + oxygen

In plants, algae and cyanobacteria, photosynthesis releases oxygen. This is called oxygenic photosynthesis. Although there are some differences between oxygenic photosynthesis in plants, algae, and cyanobacteria, the overall process is quite similar in these organisms.

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5.11H: Anoxygenic Photosynthesis

Photosynthetic reactions can be anoxygenic, thus they do not produce oxygen.

Learning Objectives

- Discuss the characteristics that classify a specific type of chlorophototrophy as anoxygenic photosynthesis

Key Points

- Anoxygenic photosynthesis produces cellular energy (ATP), without oxygen as a by-product.
- As opposed to eukaryotic organisms, which rely on chlorophylls for photosynthesis, anoxygenic organisms rely on bacteriochlorophylls.
- The electron transport chain of anoxygenic phototrophs is cyclic, meaning the electrons used during photosynthesis are fed back into the system, therefore no electrons are left over to oxidize water into oxygen.

Key Terms

- **electron transport chain**: An electron transport chain (ETC) couples electron transfer between an electron donor (such as NADH) and an electron acceptor (such as O2) with the transfer of H+ ions (protons) across a membrane. The resulting electrochemical proton gradient is used to generate chemical energy in the form of adenosine triphosphate (ATP). Electron transport chains are the cellular mechanisms used for extracting energy from sunlight in photosynthesis and also from redox reactions, such as the oxidation of sugars (respiration).
- **electron donor**: An electron donor is a chemical entity that donates electrons to another compound. It is a reducing agent that, by virtue of its donating electrons, is itself oxidized in the process.
- **anoxygenic**: That does not involve the production of oxygen

Phototrophy is the process by which organisms trap light energy (photons) and store it as chemical energy in the form of ATP and/or reducing power in NADPH. There are two major types of phototrophy: chlorophyll-based chlorophototrophy and rhodopsin-based retinalophototrophy. Chlorophototrophy can further be divided into oxygenic photosynthesis and anoxygenic phototrophy. Oxygenic and anoxygenic photosynthesizing organisms undergo different reactions either in the presence of light or with no direct contribution of light to the chemical reaction (colloquially called “light reactions” and “dark reactions”, respectively).



Figure: **Green d winogradsky**: A column containing green sulfur bacteria which uses anoxygenic photosynthesis.

Anoxygenic photosynthesis is the phototrophic process where light energy is captured and converted to ATP, without the production of oxygen. Water is therefore not used as an electron donor. There are several groups of bacteria that undergo anoxygenic photosynthesis: Green sulfur bacteria, green and red filamentous anoxygenic phototrophs (FAPs), phototrophic purple bacteria, phototrophic Acidobacteria, and phototrophic heliobacteria. Anoxygenic phototrophs have photosynthetic pigments called bacteriochlorophylls (similar to chlorophyll found in eukaryotes). Bacteriochlorophyll a and b have wavelengths of maximum absorption at 775 nm and 790 nm, respectively in ether. In vivo however, due to shared extended resonance structures, these pigments were found to maximally absorb wavelengths out further into the near-infrared. Bacteriochlorophylls c-g have the corresponding “peak” absorbance at more blue wavelengths when dissolved in an organic solvent, but are similarly red-shifted within their natural environment (with the exception of bacteriochlorophyll f, which has not been naturally observed).Unlike

oxygenic phototrophs, anoxygenic photosynthesis only functions using (by phylum) either one of two possible types of photosystem. This restricts them to cyclic electron flow and are therefore unable to produce O_2 from the oxidization of H_2O.

The cyclic nature of the electron flow is typified in purple non-sulfur bacteria. The electron transport chain of purple non-sulfur bacteria begins when the reaction centre bacteriochlorophyll pair, P870, becomes excited from the absorption of light. Excited P870 will then donate an electron to Bacteriopheophytin, which then passes it on to a series of electron carriers down the electron chain. In the process, it will generate a proton motor force (PMF) which can then be used to synthesize ATP by oxidative phosphorylation. The electron returns to P870 at the end of the chain so it can be used again once light excites the reaction-center. Therefore electrons are not left over to oxidize H_2O into O_2.

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SECTION OVERVIEW

5.12: Biosynthesis

Topic hierarchy

5.12A: Substrates for Biosysnthesis

5.12B: Biosynthesis and Energy

5.12C: The Calvin Cycle

5.12D: Intermediates Produced During the Calvin Cycle

5.12E: Regulation of the Calvin Cycle

5.12F: The Reverse TCA Cycle

5.12G: The Acetyl-CoA Pathway

5.12H: The 3-Hydroxypropionate Cycle

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5.12A: Substrates for Biosysnthesis

Major metabolic pathways require substrates to be acted upon for the formation of larger, more complex products.

Learning Objectives

- Describe the importance of substrates for biosynthesis

Key Points

- Biogenesis or anabolism, requires substrates to be acted upon that result in the formation of larger more complex molecules.
- A central metabolic pathway that produces precursors and substrates used in biosynthetic processes is the TCA cycle.
- A central metabolic pathway that produces precursors and substrates used in biosynthetic processes is glycolysis.

Key Terms

- **reducing agent**: A substance that functions in reducing or donating electrons to another substance until that specific substance becomes oxidized.
- **oxidation**: A reaction in which the atoms of an element lose electrons and the valence of the element increases.

Microorganisms have numerous pathways and processes in place to ensure both energy and nutrient production. These pathways are necessary for survival and cellular function. The major metabolic pathways require substrates to be acted upon for the formation of larger, more complex products. Biosynthetic processes are defined by the production of more complex products that are required for growth and maintenance of life. These processes require pathways that are often multi-step. There are various components deemed necessary for biosynthetic processes to occur, including: precursor compounds, chemical energy, and carious catalytic enzymes.

TCA Cycle

The citric acid cycle, commonly referred to as the Krebs cycle, is characterized by the production of energy through the oxidation of acetate derived from carbohydrates, fats, and proteins into carbon dioxide. The cycle is one of the major metabolic processes utilized to generate energy. The citric acid cycle, comprised of a series of chemical reactions, provides precursors for additional biochemical pathways. These precursors are used as substrates for the biogenesis of large complex products. The precursors include amino acids and reducing agents such as NADH. Additional pathways that require precursors formed by the TCA include amino acid and nucleotide synthesis.

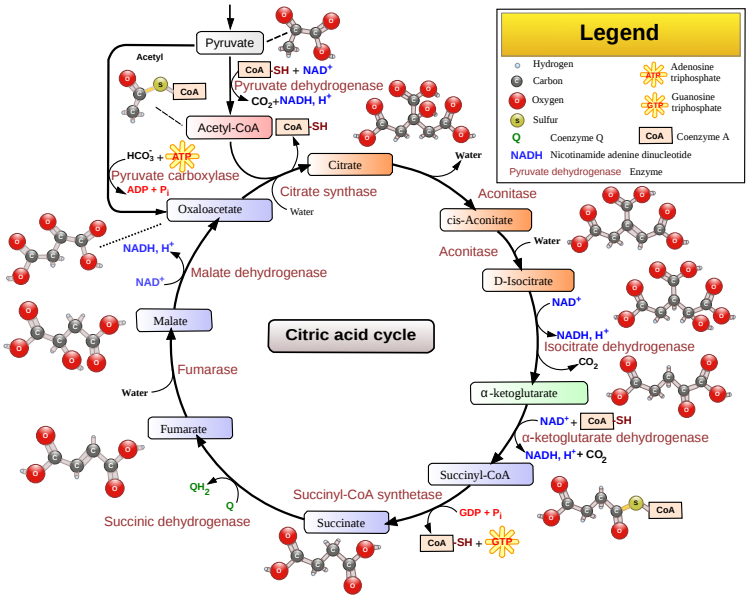

Figure: **The Citric Acid Cycle**: An overview of the Citric Acid Cycle.

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Glycolysis

An additional central metabolic pathway includes glycolysis. Glycolysis is characterized by a series of reactions that results in the conversion of glucose into pyruvate. This process is characterized by the production of various intermediates and molecules that function as substrates in additional pathways. Additional pathways that require substrates or metabolites produced by the glycolytic pathway include: gluconeogenesis, lipid metabolism, the pentose phosphate pathway, and the TCA.

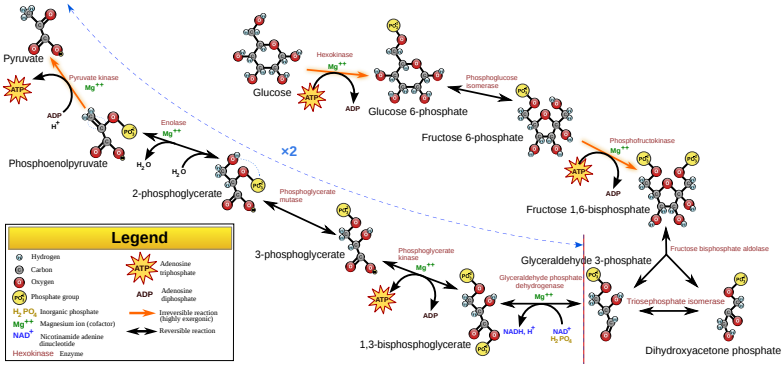

Figure: **Glycolysis Pathway Overview**: An overview of the glycolytic pathway. This pathway, comprised of a series of reactions, produces many intermediates and molecules utilized as substrates for biosynthesis in additional pathways.

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5.12B: Biosynthesis and Energy

Biosynthetic processes ensure the production of complex products necessary for cellular and metabolic processes.

Learning Objectives

- Discuss the principles of biosynthesis and provide examples

Key Points

- Anabolism is the form of metabolism responsible for building large complexes from precursors.
- The three categories of carbon fixation pathways are the Calvin cycle, the reverse TCA, and acetyl-CoA pathways.
- One example of a biosynthetic process is gluconeogenesis, which is responsible for the production of glucose from noncarbohydrate precursors.

Key Terms

- **anabolism**: Anabolism is the set of metabolic pathways that construct molecules from smaller units.
- **biosynthesis**: Biosynthesis is an enzyme-catalyzed process in cells of living organisms by which substrates are converted to more complex products.
- **metabolic**: Of or pertaining to metabolism; as, metabolic activity; metabolic force.

Biosynthesis and Energy

Biosynthesis in living organisms is a process in which substrates are converted to more complex products. The products which are produced as a result of biosynthesis are necessary for cellular and metabolic processes deemed essential for survival. Biosynthesis is often referred to as the anabolism branch of metabolism that results in complex proteins such as vitamins.

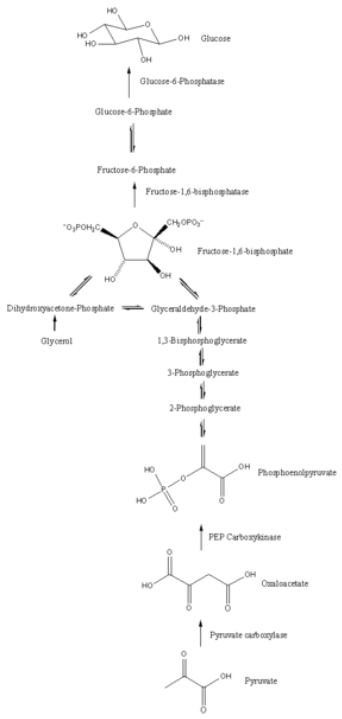

Figure: **Overview of Gluconeogenesis**: A biosynthetic pathway is utilized in microorganisms to produce glucose.

A majority of the organic compounds required by microorganisms are produced via biosynthetic pathways. The components which are utilized by biosynthetic pathways to promote the production of large molecules include chemical energy and catalytic enzymes. Biosynthetic building blocks utilized by organisms include amino acids, purines, pyrimidines, lipids, sugars, and enzyme cofactors. There are numerous mechanisms in place to ensure biosynthetic pathways are properly controlled so a cell will produce a specific amount of a compound. Biosynthetic metabolism (also known as anabolism) involves the synthesis of macromolecules from specific building blocks. A majority of these processes are considered to be multi-step or multi-enzymatic processes.

Carbon Dioxide Fixation

Carbon dioxide fixation is necessary to ensure carbon dioxide can be converted into organic carbon. The major pathways utilized to ensure fixation of carbon dioxide include: the Calvin cycle, the reductive TCA cycle, and the acetyl-CoA pathway. The Calvin cycle involves utilizing carbon dioxide and water to form organic compounds. The reductive TCA cycle, commonly referred to as the reverse Krebs cycle, also produces carbon compounds from carbon dioxide and water. In the acetyl-CoA pathway, carbon dioxide is reduced to carbon monoxide and then acetyl-CoA.

Glucose and Fructose Synthesis

An additional biosynthetic pathway utilized by microorganisms includes the synthesis of sugars and polysaccharides. The ability to synthesize sugars and polysaccharides from noncarbohydrate precursors is key to survival in numerous microorganisms. The process of gluconeogenesis, characterized by the production of glucose or fructose from noncarbohydrate precursors, is an ubiquitous process. This process utilizes precursors such as pyruvate, lactate, or glycerol.

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5.12C: The Calvin Cycle

The Calvin cycle is organized into three basic stages: fixation, reduction, and regeneration.

Learning Objectives

- Describe the Calvin Cycle

Key Points

- The Calvin cycle refers to the light-independent reactions in photosynthesis that take place in three key steps.
- Although the Calvin Cycle is not directly dependent on light, it is indirectly dependent on light since the necessary energy carriers (ATP and NADPH) are products of light-dependent reactions.
- In fixation, the first stage of the Calvin cycle, light-independent reactions are initiated; CO_2 is fixed from an inorganic to an organic molecule.
- In the second stage, ATP and NADPH are used to reduce 3-PGA into G3P; then ATP and NADPH are converted to ADP and $NADP^+$, respectively.
- In the last stage of the Calvin Cycle, RuBP is regenerated, which enables the system to prepare for more CO_2 to be fixed.

Key Terms

- **light-independent reaction**: chemical reactions during photosynthesis that convert carbon dioxide and other compounds into glucose, taking place in the stroma
- **rubisco**: (ribulose bisphosphate carboxylase) a plant enzyme which catalyzes the fixing of atmospheric carbon dioxide during photosynthesis by catalyzing the reaction between carbon dioxide and RuBP
- **ribulose bisphosphate**: an organic substance that is involved in photosynthesis, reacts with carbon dioxide to form 3-PGA

The Calvin Cycle

In plants, carbon dioxide (CO_2) enters the leaves through stomata, where it diffuses over short distances through intercellular spaces until it reaches the mesophyll cells. Once in the mesophyll cells, CO_2 diffuses into the stroma of the chloroplast, the site of light-independent reactions of photosynthesis. These reactions actually have several names associated with them. Other names for light-independent reactions include the Calvin cycle, the Calvin-Benson cycle, and dark reactions. The most outdated name is dark reactions, which can be misleading because it implies incorrectly that the reaction only occurs at night or is independent of light, which is why most scientists and instructors no longer use it.

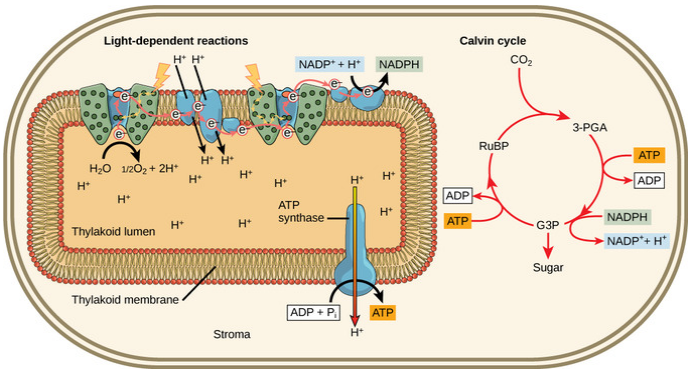

Figure: **Light Reactions**: Light-dependent reactions harness energy from the sun to produce chemical bonds, ATP, and NADPH. These energy-carrying molecules are made in the stroma where the Calvin cycle takes place. The Calvin cycle is not totally independent of light since it relies on ATP and NADH, which are products of the light-dependent reactions.

The light-independent reactions of the Calvin cycle can be organized into three basic stages: fixation, reduction, and regeneration.

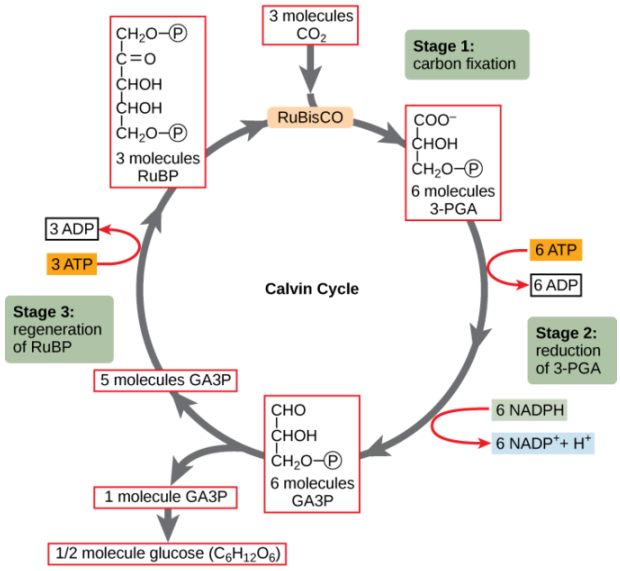

Figure: **The Calvin Cycle**: The Calvin cycle has three stages. In stage 1, the enzyme RuBisCO incorporates carbon dioxide into an organic molecule, 3-PGA. In stage 2, the organic molecule is reduced using electrons supplied by NADPH. In stage 3, RuBP, the molecule that starts the cycle, is regenerated so that the cycle can continue. Only one carbon dioxide molecule is incorporated at a time, so the cycle must be completed three times to produce a single three-carbon GA3P molecule, and six times to produce a six-carbon glucose molecule.

Stage 1: Fixation

In the stroma, in addition to CO_2,two other components are present to initiate the light-independent reactions: an enzyme called ribulose bisphosphate carboxylase (RuBisCO) and three molecules of ribulose bisphosphate (RuBP). RuBP has five atoms of carbon, flanked by two phosphates. RuBisCO catalyzes a reaction between CO_2 and RuBP. For each CO_2 molecule that reacts with one RuBP, two molecules of 3-phosphoglyceric acid (3-PGA) form. 3-PGA has three carbons and one phosphate. Each turn of the cycle involves only one RuBP and one carbon dioxide and forms two molecules of 3-PGA. The number of carbon atoms remains the same, as the atoms move to form new bonds during the reactions (3 atoms from $3CO_2$ + 15 atoms from 3RuBP = 18 atoms in 3 atoms of 3-PGA). This process is called carbon fixation because CO_2 is "fixed" from an inorganic form into organic molecules.

Stage 2: Reduction

ATP and NADPH are used to convert the six molecules of 3-PGA into six molecules of a chemical called glyceraldehyde 3-phosphate (G3P). This is a reduction reaction because it involves the gain of electrons by 3-PGA. Recall that a reduction is the gain of an electron by an atom or molecule. Six molecules of both ATP and NADPH are used. For ATP, energy is released with the loss of the terminal phosphate atom, converting it to ADP; for NADPH, both energy and a hydrogen atom are lost, converting it into $NADP^+$. Both of these molecules return to the nearby light-dependent reactions to be reused and reenergized.

Stage 3: Regeneration

At this point, only one of the G3P molecules leaves the Calvin cycle and is sent to the cytoplasm to contribute to the formation of other compounds needed by the plant. Because the G3P exported from the chloroplast has three carbon atoms, it takes three "turns" of the Calvin cycle to fix enough net carbon to export one G3P. But each turn makes two G3Ps, thus three turns make six G3Ps. One is exported while the remaining five G3P molecules remain in the cycle and are used to regenerate RuBP, which enables the system to prepare for more CO_2 to be fixed. Three more molecules of ATP are used in these regeneration reactions.

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5.12D: Intermediates Produced During the Calvin Cycle

The Calvin Cycle involves the process of carbon fixation to produce organic compounds necessary for metabolic processes.

Learning Objectives

- Outline the function of the intermediates produced in the major phases of the Calvin Cycle

Key Points

- The Calvin Cycle can be divided into three major phases: Phase 1: carbon fixation; Phase 2: reduction; Phase 3: regeneration.
- The intermediates of the Calvin Cycle include ADP, NADP+, inorganic phosphate, and 3-phosphoglycerate.
- Many of the intermediates or products of the Calvin Cycle are regenerated back into earlier stages of the process.

Key Terms

- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **coenzyme**: Any small molecule that is necessary for the functioning of an enzyme.
- **phosphorylation**: The process of transferring a phosphate group from a donor to an acceptor; often catalysed by enzymes

The Calvin Cycle is characterized as a carbon fixation pathway. The Calvin Cycle is also referred to as the reductive pentose phosphate cycle or the Calvin-Benson-Bassham cycle. The process of carbon fixation involves the reduction of carbon dioxide to organic compounds by living organisms. The Calvin cycle is most often associated with carbon fixation in autotrophic organisms, such as plants, and is recognized as a dark reaction. In organisms that require carbon fixation, the Calvin cycle is a means to obtain energy and necessary components for growth. Some examples of microorganisms that utilize the Calvin cycle include cyanobacteria, purple bacteria, and nitrifying bacteria. Specifically, the Calvin cycle involves reducing carbon dioxide to the sugar triose phosphate, most commonly known as glyceraldehyde 3-phosphate (GAP). Throughout the Calvin Cycle, there are numerous intermediate molecules made which are consistently withdrawn and utilized to create cellular material and participate in cellular processes. The Calvin cycle can be divided into three major phases which include: Phase 1: carbon fixation; Phase 2: reduction; and Phase 3: regeneration of ribulose. The following is a brief overview of the intermediates created during the Calvin cycle.

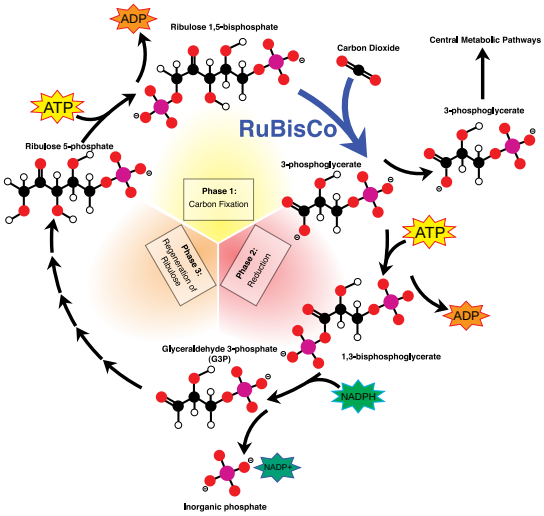

Figure: **The Calvin Cycle**: An overview of the Calvin Cycle.

Phase 1: Carbon Fixation Intermediates

During phase 1 of this cycle, the CO2 molecule is incorporated into one of two 3-phosphoglycerate molecules (3-PGA). This process requires the enzyme RuBisCO and both ATP and NADPH. Once 3-PGA is formed, one of two molecules formed continues into the reduction phase (phase 2). The additional 3-PGA is utilized in additional metabolic pathways such as glycolysis and gluconeogenesis. The structure of 3-PGA allows it to be combined and rearranged to form sugars which can be transported to additional cells or stored for energy.

Phase 2: Reduction

During phase 2 of this cycle, the newly formed 3-PGA undergoes phosphorylation by the enzyme phosphoglycerate kinase which utilizes ATP. The result of this phosphorylation is the production of 1,3-bisphosphoglycerates and ADP products. The ADP product that is produced via the breakdown of ATP will be utilized in additional pathways and be converted back into ATP. The inter conversions of ATP to ADP and ADP to ATP is a key process in supplying energy in numerous processes. This energy is necessary for cellular growth and metabolic processes.

Once the bisphosphoglycerate molecules are formed, they must be converted and further reduced to GAP by NADPH. The intermediate of this product is the conversion of NADPH to NADP+ and an inorganic phosphate ion. NADP+ is a coenzyme which is necessary for the function of NADPH. The functions that require NADP+ include anabolic reactions such as lipid and nucleic acid synthesis. The inorganic phosphate ion is often a result of regulatory metabolic processes. The phosphate ions are used in processes such as buffering cells, conversions of AMP/ADP to ATP and production of materials involved in structure such as bone and teeth. It is important to note that these intermediates or products (inorganic phosphate, NADP+ and ADP) processed by phase 2 are often regenerated back into the cycle.

Phase 3: Regeneration of Ribulose

The GAP molecules at this point are the end product of the Calvin cycle, which is responsible for reducing carbon to a sugar form. However, additional GAP molecules that are formed will be converted to ribulose-1,5-bisphosphate (RuBP), which is responsible for the conversion of CO2 to 3-PGA in phase 1, via numerous steps. The G3P, which is destined to exit the cycle, will be used for carbohydrate synthesis and additional pathways.

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5.12E: Regulation of the Calvin Cycle

Learning Objectives

- Outline the three major phases of the Calvin cycle: carbon fixation, reduction, and regeneration of ribulose

The Calvin cycle is a process utilized to ensure carbon dioxide fixation. In this process, carbon dioxide and water are converted into organic compounds that are necessary for metabolic and cellular processes. There are various organisms that utilize the Calvin cycle for production of organic compounds including cyanobacteria and purple and green bacteria. The Calvin cycle requires various enzymes to ensure proper regulation occurs and can be divided into three major phases:

1. carbon fixation,
2. reduction, and
3. regeneration of ribulose.

Each of these phases are tightly regulated and require unique and specific enzymes.

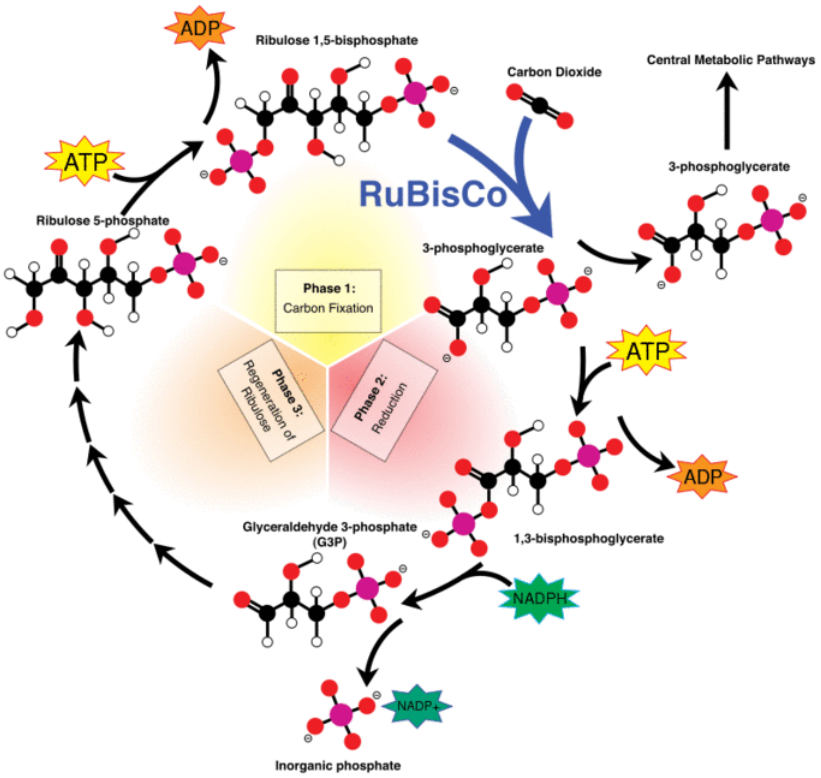

Figure: ***Figure 5.12E. 1:*** *Overview of the Calvin cycle. An overview of the Calvin cycle and the three major phases. (CC SA-BY 3.0; Mike Jones).*

During the first phase of the Calvin cycle, carbon fixation occurs. The carbon dioxide is combined with ribulose 1,5-bisphosphate to form two 3-phosphoglycerate molecules (3-PG). The enzyme that catalyzes this specific reaction is ribulose bisphosphate carboxylase (RuBisCO). RuBisCO is identified as the most abundant enzyme on earth, to date. RuBisCO is the first enzyme utilized in the process of carbon fixation and its enzymatic activity is highly regulated. RuBisCO is only active during the day as its substrate, ribulose 1,5-bisphosphate, is not generated in the dark. RuBisCO enzymatic activity is regulated by numerous factors including: ions, RuBisCO activase, ATP /ADP and reduction/oxidation states, phosphate and carbon dioxide. The various factors influencing RuBisCO activity directly affect phase 1 of the Calvin cycle.

During the second phase of the Calvin cycle, reduction occurs. The 3-PG molecules synthesized in phase 1 are reduced to glyceraldehyde-3-phosphate (G3P). This reducing process is mediated by both ATP and NADPH. One of the two G3P molecules formed are further converted to dihydroxyacetone phosphate (DHAP) and the enzyme aldolase is used to combine G3P and DHAP to form fructose-1,6-bisphosphate. The enzyme aldolase is typically characterized as a glycolytic enzyme with the ability to split fructose 1,6-bisphosphate into DHAP and G3P. However, in this specific phase of the Calvin cycle, it is used in reverse. Therefore,

aldolase is said to regulate a reverse reaction in the Calvin cycle. Additionally, aldolase can be utilized to promote a reverse reaction in gluconeogenesis as well. The fructose-1,6-bisphosphate formed in phase 2 is then converted into fructose-6-phosphate.

During the third phase of the Calvin cycle, regeneration of RuBisCO occurs. This specific phase involves a series of reactions in which there are a variety of enzymes required to ensure proper regulation. This phase is characterized by the conversion of G3P, which was produced in earlier phase, back to ribulose 1,5-bisphosphate. This process requires ATP and specific enzymes. The enzymes involved in this process include: triose phosphate isomerase, aldolase, fructose-1,6-bisphosphatase, transketolase, sedoheptulase-1,7-bisphosphatase, phosphopentose isomerase, phosphopentose epimerase, and phosphoribulokinase. The following is a brief summary of each enzyme and its role in the regeneration of ribulose 1,5-bisphosphate in the order it appears in this specific phase.

1. Triose phosphate isomerase: converts all G3P molecules into DHAP
2. Aldolase and fructose-1,6-bisphosphatase: converts G3P and DHAP into fructose 6-phosphate
3. Transketolase: removes two carbon molecules in fructose 6-phosphate to produce erythrose 4-phosphate (E4P); the two removed carbons are added to G3P to produce xylulose-5-phosphate (Xu5P)
4. Aldolase: converts E4P and a DHAP to sedoheptulose-1,7-bisphosphate
5. Sedoheptulase-1,7-bisphosphatase: cleaves the sedohetpulose-1,7-bisphosphate into sedoheptulase-7-phosphate (S7P)
6. Transketolase: removes two carbons from S7P and two carbons are transferred to one of the G3P molecules producing ribose-5-phosphate (R5P)and another Xu5P
7. Phosphopentose isomerase: converts the R5P into ribulose-5-phosphate (Ru5P)
8. Phosphopentose epimerase: converts the Xu5P into Ru5P
9. Phosphoribulokinase: phosphorylates Ru5P into ribulose-1,5-bisphosphate

After this final enzyme performs this conversion, the Calvin cycle is considered complete. The regulation of the Calvin cycle requires many key enzymes to ensure proper carbon fixation.

Key Points

- In this process, carbon dioxide and water are converted into organic compounds that are necessary for metabolic and cellular processes.
- The three phases of the Calvin cycle, fixation, reduction, and regeneration require specific enzymes to ensure proper regulation.
- The last phase of the Calvin cycle, regeneration, is considered the most complex and regulated phase of the cycle.

Key Terms

- **calvin cycle**: A series of biochemical reactions that take place in the stroma of chloroplasts in photosynthetic organisms.
- **gluconeogenesis**: A metabolic process which glucose is formed from non-carbohydrate precursors.
- **ribulose**: A ketopentose whose phosphate derivatives participate in photosynthesis.

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5.12F: The Reverse TCA Cycle

The reverse TCA cycle utilizes carbon dioxide and water to form carbon compounds.

Learning Objectives

- List the enzymes and function that are unique to the reverse TCA cycle (ATP citrate lyase; 2-oxoglutarate:ferredoxin oxidoreductase; pyruvate:ferredoxin oxidoreductase)

Key Points

- The TCA cycle utilizes complex carbon molecules and oxidizes them to carbon dioxide and water.
- The reverse TCA utilizes carbon dioxide and water to produce carbon molecules.
- There are three major enzymes that are unique to reverse TCA including ATP citrate lyase which converts citrate into oxaloacetate and acetyl CoA.

Key Terms

- **Krebs cycle**: A series of enzymatic reactions that occurs in all aerobic organisms; it involves the oxidative metabolism of acetyl units and serves as the main source of cellular energy.
- **ATP citrate lyase**: ATP citrate lyase is an enzyme that represents an important step in fatty acid biosynthesis. This step in fatty acid biosynthesis occurs because ATP citrate lyase is the link between the metabolism of carbohydrates (which causes energy) and the production of fatty acids.
- **carboxylation**: A reaction that introduces a carboxylic acid into a molecule.

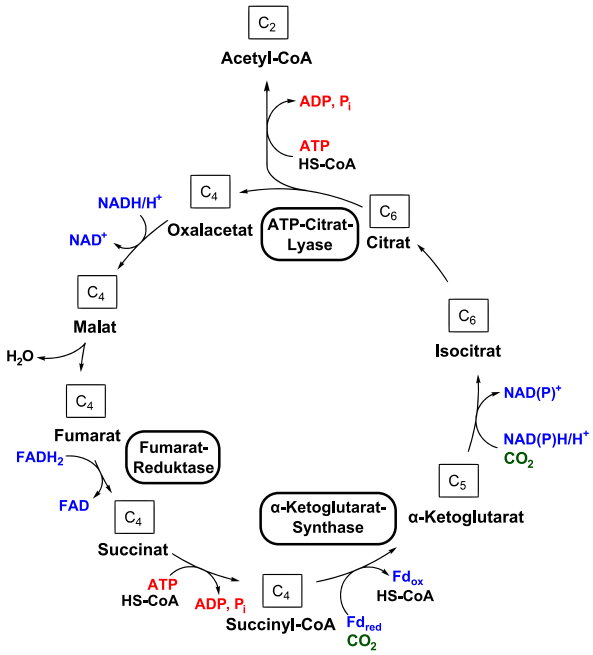

Figure: **The Reverse Citric Acid Cycle**: An overview of the reverse citric acid cycle.

The citric acid cycle (TCA) or Krebs cycle, is a process utilized by numerous organisms to generate energy via the oxidation of acetate derived from carbohydrates, fats, and proteins into carbon dioxide. The cycle plays a critical role in the maintenance of numerous central metabolic processes. However, there are numerous organisms that undergo reverse TCA or reverse Krebs cycles. This process is characterized by the production of carbon compounds from carbon dioxide and water. The chemical reactions that occur are the reverse of what is seen in the TCA cycle. There are numerous anaerobic organisms that utilize a cyclic reverse TCA cycle and an example includes organisms classified as Thermoproteus. The following is a brief overview of the reverse TCA cycle.

Reverse TCA Summary

The reverse TCA cycle is a series of chemical reactions by which organisms produce carbon compounds from carbon dioxide and water. The reverse TCA cycle requires electron donors and often times, bacteria will use hydrogen, sulfide or thiosulfate for this purpose. The reverse TCA is considered to be an alternative to photosynthesis which produces organic molecules as well. Reverse TCA, a form of carbon fixation, utilizes numerous ATP molecules, hydrogen and carbon dioxide to generate an acetyl CoA. This process requires a number of reduction reactions using various carbon compounds. The enzymes, unique to reverse TCA, that function in catalyzing these reactions include: ATP citrate lyase, 2-oxoglutarate:ferredoxin oxidoreductase, and pyruvate:ferredoxin oxidoreductase. ATP citrate lyase is one of the key enzymes that function in reverse TCA. ATP citrate lyase is the enzyme responsible for cleaving citrate into oxaloacetate and acetyl CoA. These enzymes are unique to reverse TCA and are necessary for the reductive carboxylation to occur.

In reverse TCA, the following occurs in a cyclic manner:

1) oxaloacetate is converted to malate (NADH/H+ is utilized and NAD+ is produced)

2) malate is converted to fumarate (H20 molecule is produced)

3) fumarate is converted to succinate via a fumarate-reductase enzyme ($FADH_2$ is converted to FAD)

4) succinate is converted to succinyl-CoA (ATP is hydrolyzed to ADP+Pi)

5) succincyl CoA is converted to alpha-ketoglutarate via an alpha-ketoglutarate synthase (reduction of carbon dioxide occurs and oxidation of coenzyme A)

6) alpha-ketoglutarate is converted to isocitrate (NAD(P)H/H+ and CO_2 is broken down to NAD(P+)

7) isocitrate is converted to citrate

8) ATP citrate lyase is then used to convert citrate to oxaloacetate and acetyl CoA (ATP is hydrolyzed to ADP and Pi).

9) Pathway is cyclic and continues cycle from step 1

An example of a microorganism that utilizes reverse TCA includes Thermoproteus. Thermoproteusis type of prokaryotic that is characterized as a hydrogen-sulfur autotroph. The organisms classified as Thermoproteus utilizes sulfur reduction for metabolic processes. As previously mentioned, organisms that use reverse TCA may use sulfur as an electron donor to carry out this metabolic process.

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5.12G: The Acetyl-CoA Pathway

The acetyl-CoA pathway utilizes carbon dioxide as a carbon source and often times, hydrogen as an electron donor to produce acetyl-CoA.

Learning Objectives

- Describe the role of the carbon monoxide dehydrogenase and acetyl-CoA synthetase in the acetyl-CoA pathway

Key Points

- The acetyl-CoA pathway utilizes two major enzymes in the production of acetyl-CoA: carbon monoxide dehydrogenase and acetyl-CoA synthase.
- Carbon monoxide dehydrogenase functions in the reduction of carbon dioxide to a methyl group.
- Acetyl-CoA synthase functions in combining carbon monoxide and a methyl group to produce acetyl-CoA.

Key Terms

- **acetogenesis**: The anaerobic production of acetic acid or acetate by bacteria.

The acetyl coenzyme A (CoA) pathway, commonly referred to as the Wood-Ljungdahl pathway or the reductive acetyl-CoA pathway, is one of the major metabolic pathways utilized by bacteria. This specific pathway is characterized by the use of hydrogen as an electron donor and carbon dioxide as an electron acceptor to produce acetyl-CoA as the final product. Acetyl-CoA is a major component in numerous metabolic processes as it plays a key role in the citric acid cycle. The main function of acetyl-CoA in the citric cycle is to transport carbon atoms. In regards to molecular structure, acetyl-CoA functions as the thioester between conezyme A and acetic acid. Specific types of organisms that utilize this pathway include archaea classified as methanogens and acetate-producing bacteria as well. The following is a brief overview of the acetyl-CoA pathway..

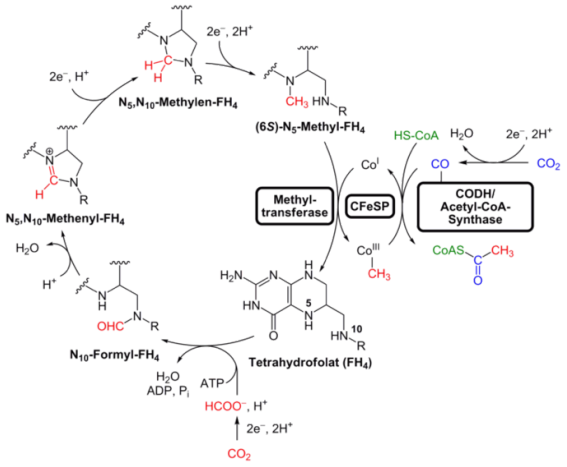

Figure: **Acetyl-CoA Pathway**: An overview of the acetyl-CoA pathway

The acetyl-CoA pathway begins with the reduction of a carbon dioxide to carbon monoxide. The other carbon dioxide is reduced to a carbonyl group. The two major enzymes involved in these processes are carbon monoxide dehydrogenase and acetyl CoA synthase complex. The carbon dioxide that is reduced to a carbonyl group, via the carbon monoxide dehydrogenase, is combined with the methyl group to form acetyl-CoA. The acetyl-CoA synthase complex is responsible for this reaction.

Carbon Monoxide Dehydrogenase

Carbon monoxide dehydrogenase, the enzyme responsible for the reduction of a carbon dioxide to a carbonyl group, functions in numerous biochemical processes. These processes include metabolism of methanogens, acetogenic and sulfate-reducing bacteria. Specifically, the acetyl-CoA pathway is utilized by bacteria that are classified as methanogens and acetate-producing organisms. The carbon monoxide dehydrogenase allows organisms to use carbon dioxide as a source of carbon and carbon monoxide as a source of energy.The carbon monoxide dehydrogenase can also form a complex with the acetyl-CoA synthase complex which is key in the acetyl-CoA pathway.

Acetyl-CoA Synthetase

Acetyl-CoA synthetase is a class of enzymes that is key to the acetyl-CoA pathway. The acetyl-CoA synthetase functions in combining the carbon monoxide and a methyl group to produce acetyl-CoA..

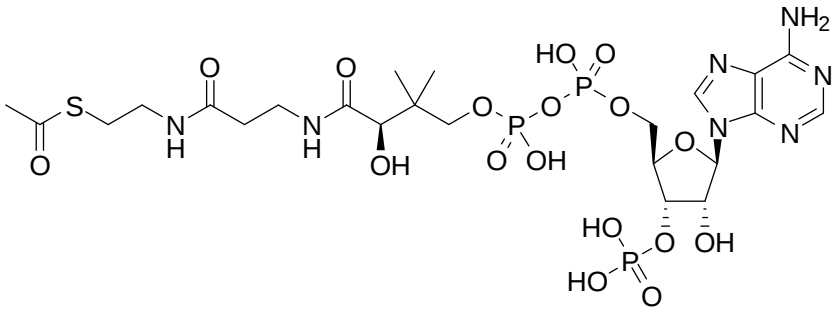

Figure: **Acetyl-CoA Structure**: Schematic of the structure of acetyl-CoA

Microorganisms and the Acetyl-CoA Pathway

The ability to utilize the acetyl-CoA pathway is advantageous due to the ability to utilize both hydrogen and carbon dioxide to produce acetyl-CoA. Specific types of bacteria which utilize the acetyl-CoA pathway include methanogens and acetate-producing bacteria.

Methanogens

Methanogens are types of organisms, classified as archaea, that exhibit the ability to produce methane as a metabolic byproduct. Methanogens, which are found in numerous environments including wetlands, marine sediments, hot springs and hydrothermal vents, are able to use carbon dioxide as a source of carbon for growth. In addition, the carbon dioxide is used as an electron acceptor in the production of methane. Methanogens are able to utilize the acetyl-CoA pathway to fix carbon dioxide.

Acetogens

Acetate producing bacteria, or acetogens, are a class of microorganisms that are able to generate acetate as a product of anaerobic respiration. This process, known as acetogenesis, will occur in organisms that are typically found in anaerobic environments. Acetogens are able to use carbon dioxide as a source of carbon and hydrogen as a source of energy.

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5.12H: The 3-Hydroxypropionate Cycle

Learning Objectives

- Recall the two major phases and known steps in the 3-hydroxypropionate cycle

Carbon fixation is a key pathway in numerous microorganisms, resulting in the formation of organic compounds deemed necessary for cellular processes. One of the pathways that is utilized for carbon fixation is the 3-hydroxypropionate cycle. Specifically, in this cycle, the carbon dioxide is fixed by acetyl-CoA and propionyl-CoA carboxylases. This process results in the formation of malyl-CoA which is further split into acetyl-CoA and glyoxylate. Propionyl-CoA carboxylase is an enzyme that functions in the carboxylation of propionyl CoA. This enzyme functions in the mitochondrial matrix and is biotin dependent. The acetyl-CoA carboxylase utilized in this cycle is biotin-dependent as well and catalyzes the carboxylation of acetyl-CoA to malonyl-CoA.

This pathway produces pyruvate via conversion of bicarbonate and also results in the production of intermediates such as acetyl-CoA, gloxylate and succinyl-CoA. To date, this pathway has been identified in organisms classified as green non sulfur bacteria, specifically *Chloroflexus aurantiacus ()* and in chemotrophic archaea. The green non sulfur bacteria uses reduced sulfur compounds, such as hydrogen sulfide or thiosulfate as an electron donor for metabolism. The ability of *Chloroflexus aurantiacus* to utilize this pathway is unique. The 3-hydroxypropionate cycle is a newly discovered pathway, thus, the exact details involving this process in regards to enzymes and intracellular components are still currently under investigation. However, the cycle can be broken down into two major phases, carbon dioxide fixation and glyoxylate assimilation. Glyoxylate, the conjugate base of glyoxylic acid, is the form that exists at a neutral pH. The importance of glyoxylate within microorganisms is in its ability to convert fatty acids into carbohydrates. Numerous types of organisms including bacteria, fungi and plants can utilize glyoxylate for these processes.

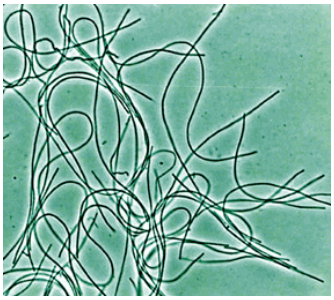

Figure: ***Chloroflexus aurantiacus****: An image of Chloroflexus aurantiacus, a green nonsulfur bacteria that utilizes the 3-hydroxypropionate pathway.*

Key Points

- The 3-hydroxypropionate cycle is a newly identified pathway and many of the exact details which occur are currently under investigation.
- This pathway is utilized in green non sulfur bacteria such as Chloroflexus aurantiacus.
- The pathway can be divided into major phases which includes carbon dioxide fixation and gloxylate assimilation.

Key Terms

- **glyoxylate**: a salt or ester of glyoxylic acid
- **carboxylation**: A reaction that introduces a carboxylic acid into a molecule.

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SECTION OVERVIEW

5.13: Anabolism

Topic hierarchy

5.13A: Polysaccharide Biosynthesis

5.13B: Lipid Biosynthesis

5.13C: Regulation by Biosynthetic Enzymes

5.13D: Bacterial Polyesters

5.13E: Polyketide Antibiotics

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5.13A: Polysaccharide Biosynthesis

Polysaccharides are synthesized from two forms of activated glucose molecules: UDP-glucose and ADP-glucose.

Learning Objectives

- Describe the mechanism of polysaccharide biosynthesis and its importance in bacteria

Key Points

- Uridine diphosphate glucose (UDP-glucose) is a nucleotide sugar. UDP-glucose consists of the pyrophosphate group, the pentose sugar ribose, glucose, and the nucleobase uracil. It is used as a substrate for enzymes called glucosyltransferases.
- UDP-glucose can also be used as a precursor of lipopolysaccharides, and peptidoglycan. ADP-glucose is usually the precursor for glycogen production in bacteria.
- When the cells are grown on a carbon source different than glucose, gluconeogenesis (abbreviated GNG) is the metabolic pathway used to produce glucose from non- carbohydrate carbon substrates such as phosphoenolpyruvate (PEP).
- Pathogenic bacteria can produce a thick, mucous-like, layer of polysaccharide. This “capsule” cloaks antigenic proteins on the bacterial surface. Bacteria and other microbes, secrete polysaccharides as an evolutionary adaptation to help them adhere to surfaces and to prevent them from drying out.

Key Terms

- **Polysaccharides**: Polysaccharides are long, carbohydrate molecules of repeated monomer units joined together by glycosidic bonds. They range in structure from linear to highly branched. Polysaccharides are often quite heterogeneous, containing slight modifications of the repeating unit.
- **gluconeogenesis**: Gluconeogenesis (abbreviated GNG) is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as pyruvate, lactate, glycerol, and glucogenic amino acids.
- **glucosyltransferases**: Glucosyltransferases are a type of glycosyltransferase that enable the transfer of glucose such as glycogen synthesis.

Polysaccharides are long carbohydrate molecules of repeated monomer units joined together by glycosidic bonds. They range in structure from linear to highly branched. Polysaccharides are often quite heterogeneous, containing slight modifications of the repeating unit. Depending on the structure, these macromolecules can have distinct properties from their monosaccharide building blocks. They may be amorphous or even insoluble in water.

One of the most common building block of polysaccharides is glucose. However, glucose has to be in its activated forms. There are two forms of activated glucose: UDP-glucose and ADP-glucose.

Uridine diphosphate glucose (uracil-diphosphate glucose, UDP-glucose) is a nucleotide sugar. Components UDP-glucose consists of the pyrophosphate group, the pentose sugar ribose, glucose, and the nucleobase uracil. It is used in nucleotide sugars metabolism as an activated form of glucose as a substrate for enzymes called glucosyltransferases. UDP-glucose can also be used as a precursor of lipopolysaccharides, and peptidoglycan. ADP-glucose is usually the precursor for glycogen production in bacteria.

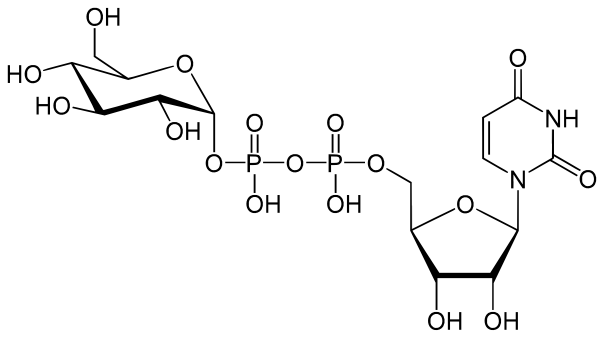

Figure: **Structure of UDP-glucose**: UDP-Glucose consists of the pyrophosphate group, the pentose sugar ribose, glucose, and the nucleobase uracil.

When the cells are grown on a carbon source different than glucose, then polysaccharides are synthesized using a different pathway. Gluconeogenesis (abbreviated GNG) is a metabolic pathway that results in the generation of glucose from non-

carbohydrate carbon substrates such as phosphoenolpyruvate (PEP). PEP is formed from the decarboxylation of oxaloacetate and hydrolysis of one guanosine triphosphate molecule. This reaction is a rate-limiting step in gluconeogenesis.

Pathogenic bacteria commonly produce a thick, mucous-like, layer of polysaccharide. This “capsule” cloaks antigenic proteins on the bacterial surface that would otherwise provoke an immune response and thereby lead to the destruction of the bacteria. Bacteria and many other microbes, including fungi and algae, often secrete polysaccharides as an evolutionary adaptation to help them adhere to surfaces and to prevent them from drying out. Humans have developed some of these polysaccharides into useful products including xanthan gum, dextran, welan gum, gellan gum, diutan gum, and pullulan.

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5.13B: Lipid Biosynthesis

Many of the immune activating abilities of lipopolysaccharide can be attributed to the lipid A unit.

Learning Objectives

- Outline the characteristics and processes of lipid biosynthesis, including:; lipogenesis and fatty acid biosynthesis

Key Points

- Lipid A is a lipid component of an endotoxin held responsible for toxicity of Gram-negative bacteria.
- The synthesis of unsaturated fatty acids involves a desaturation reaction, whereby a double bond is introduced into the fatty acyl chain.
- In archaea, the mevalonate pathway produces reactive precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate from acetyl-CoA, while in plants and bacteria the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates.

Key Terms

- **lipid A**: Lipid A is a lipid component of an endotoxin held responsible for toxicity of Gram-negative bacteria. It is the innermost of the three regions of the lipopolysaccharide (LPS, also called endotoxin) molecule, and its hydrophobic nature allows it to anchor the LPS to the outer membrane.
- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.
- **lipogenesis**: The biochemical production of fat, especially the conversion of carbohydrate into fat so that it may be stored as a long-term source of energy when food is scarce.

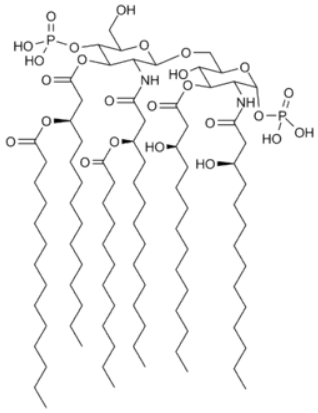

Figure: **Chemical structure of lipid A as found in E. coli**: Chemical structure of lipid A as found in E. coli

Lipids constitute a broad group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, and others. The main biological functions of lipids include energy storage, as structural components of cell membranes, and as important signaling molecules.

Lipids may be broadly defined as hydrophobic or amphiphilic small molecules. The amphiphilic nature of some lipids allows them to form structures such as vesicles, liposomes, or membranes in an aqueous environment. Biological lipids originate entirely or in part from two distinct types of biochemical subunits or “building-blocks”: ketoacyl and isoprene groups. Using this approach, lipids may be divided into eight categories: fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, and polyketides (derived from condensation of ketoacyl subunits); and sterol lipids and prenol lipids (derived from condensation of isoprene subunits).

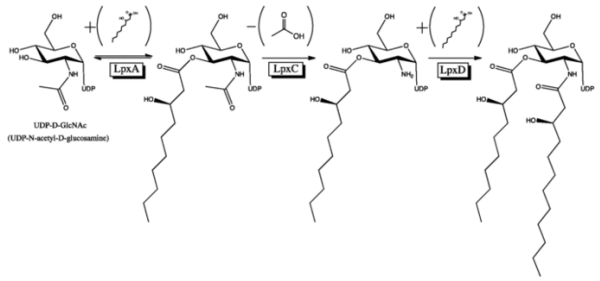

Figure: **Synthesis of the UDP-diacylglucosamine precursor of Lipid A**: Synthesis of the UDP-diacylglucosamine precursor of Lipid AThe synthesis of unsaturated fatty acids involves a desaturation reaction, whereby a double bond is introduced into the fatty acyl chain. For example, in humans, the desaturation of stearic acid by stearoyl-CoA desaturase-1 produces oleic acid. The doubly unsaturated fatty acid linoleic acid as well as the triply unsaturated α-linolenic acid cannot be synthesized in mammalian tissues, and are therefore essential fatty acids and must be obtained from the diet. Triglyceride synthesis takes place in the endoplasmic reticulum by metabolic pathways in which acyl groups in fatty acyl-CoAs are transferred to the hydroxyl groups of glycerol-3-phosphate and diacylglycerol. Terpenes and isoprenoids, including the carotenoids, are made by the assembly and modification of isoprene units donated from the reactive precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate. These precursors can be made in different ways. In archaea, the mevalonate pathway produces these compounds from acetyl-CoA, while in plants and bacteria the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates.

Although humans and other mammals use various biosynthetic pathways to both break down and synthesize lipids, some essential lipids cannot be made this way and must be obtained from the diet.

In animals, when there is an oversupply of dietary carbohydrate, the excess carbohydrate is converted to triglycerides. This involves the synthesis of fatty acids from acetyl-CoA and the esterification of fatty acids in the production of triglycerides, a process called lipogenesis. Fatty acids are made by fatty acid synthases that polymerize and then reduce acetyl-CoA units. The acyl chains in the fatty acids are extended by a cycle of reactions that add the acetyl group, reduce it to an alcohol, dehydrate it to an alkene group and then reduce it again to an alkane group.

The enzymes of fatty acid biosynthesis are divided into two groups, in animals and fungi all these fatty acid synthase reactions are carried out by a single multifunctional protein, while in plant plastids and bacteria separate enzymes perform each step in the pathway. The fatty acids may be subsequently converted to triglycerides that are packaged in lipoproteins and secreted from the liver.

One important reaction that uses these activated isoprene donors is steroid biosynthesis. Here, the isoprene units are joined together to make squalene and then folded up and formed into a set of rings to make lanosterol. Lanosterol can then be converted into other steroids such as cholesterol and ergosterol.

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5.13C: Regulation by Biosynthetic Enzymes

Attenuation is a regulatory feature found throughout Archaea and Bacteria domains which causes premature termination of transcription.

Learning Objectives

- Discuss how attenuation can regulate expression of biosynthetic enzymes

Key Points

- Attenuators may be classified according to the type of molecule that induces the change in RNA structure.
- Attenuator is a nucleotide sequence in DNA that can lead to premature termination of transcription.
- An example of attenuation is the trp gene in bacteria.

Key Terms

- **transcription**: The synthesis of RNA under the direction of DNA.
- **termination**: The process of terminating or the state of being terminated.
- **Attenuation**: Attenuation (in genetics) is a proposed mechanism of control in some bacterial operons that results in premature termination of transcription. It is based on the fact that, in bacteria, transcription and translation can and do proceed simultaneously.

Attenuation (in genetics) is a proposed mechanism of control in some bacterial operons that results in premature termination of transcription. It is based on the fact that, in bacteria, transcription and translation can and do proceed simultaneously. Attenuation involves a provisional stop signal (attenuator), located in the DNA segment that corresponds to the leader sequence of mRNA. During attenuation, the ribosome becomes stalled (delayed) in the attenuator region in the mRNA leader. Depending on the metabolic conditions, the attenuator either stops transcription at that point or allows read-through to the structural gene part of the mRNA and synthesis of the appropriate protein.

Attenuation is a regulatory feature found throughout Archaea and Bacteria causing premature termination of transcription. Attenuators are 5′-cis acting regulatory regions that fold into one of two alternative RNA structures that determine the success of transcription. The folding is modulated by a sensing mechanism producing either a Rho-independent terminator, resulting in interrupted transcription and a non-functional RNA product; or an anti-terminator structure, resulting in a functional RNA transcript. There are now many equivalent examples where the translation, not transcription, is terminated by sequestering the Shine-Dalgarno sequence (ribosomal binding site) in a hairpin-loop structure. While not meeting the previous definition of (transcriptional) attenuation, these are now considered to be variants of the same phenomena and are included in this article. Attenuation is an ancient regulatory system, prevalent in many bacterial species providing fast and sensitive regulation of gene operons and is commonly used to repress genes in the presence of their own product (or a downstream metabolite). What is an attenuator? Attenuator is a nucleotide sequence in DNA that can lead to premature termination of transcription.

Attenuators may be classified according to the type of molecule which induces the change in RNA structure. It is likely that transcription-attenuation mechanisms developed early, perhaps prior to the archaea/bacteria separation and have since evolved to use a number of different sensing molecules (the tryptophan biosynthetic operon has been found to use three different mechanisms in different organisms.)

An example is the trp gene in bacteria. When there is a high level of tryptophan in the region, it is inefficient for the bacterium to synthesize more. When the RNA polymerase binds and transcribes the trp gene, the ribosome will start translating. (This differs from eukaryotic cells, where RNA must exit the nucleus before translation starts.) The attenuator sequence, which is located between the mRNA leader sequence (5′ UTR) and trp operon gene sequence, contains four domains, where domain 3 can pair with domain 2 or domain 4.

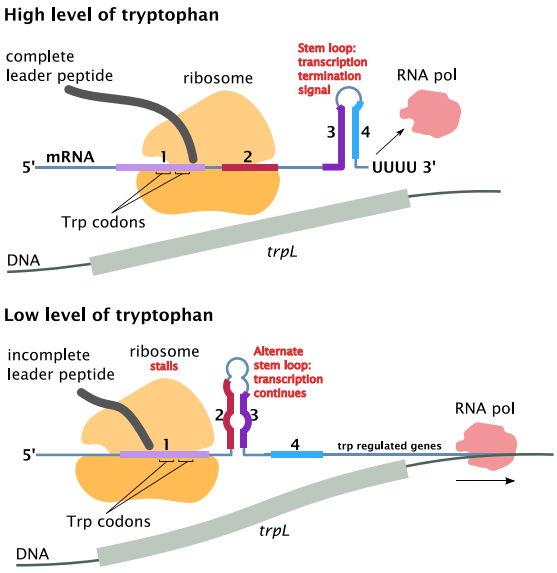

Figure: **Mechanism of transcriptional attenuation of the trp operon.**: Mechanism of transcriptional attenuation of the trp operon.

The attenuator sequence at domain 1 contains instruction for peptide synthesis that requires tryptophans. A high level of tryptophan will permit ribosomes to translate the attenuator sequence domains 1 and 2, allowing domains 3 and 4 to form a hairpin structure, which results in termination of transcription of the trp operon. Since the protein coding genes are not transcribed due to rho independent termination, no tryptophan is synthesized.

In contrast, a low level of tryptophan means that the ribosome will stall at domain 1, causing the domains 2 and 3 to form a different hairpin structure that does not signal termination of transcription. Therefore, the rest of the operon will be transcribed and translated, so that tryptophan can be produced. Thus, domain 4 is an attenuator. Without domain 4, translation can continue regardless of the level of tryptophan. The attenuator sequence has its codons translated into a leader peptide, but is not part of the trp operon gene sequence. The attenuator allows more time for the attenuator sequence domains to form loop structures, but does not produce a protein that is used in later tryptophan synthesis.

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5.13D: Bacterial Polyesters

Polyhydroxyalkanoates or PHAs are linear polyesters produced in nature by bacterial fermentation of sugar or lipids.

Learning Objectives

- Summarize the process of PHA production and its applications

Key Points

- To produce PHA, a culture of a micro- organism such as Alcaligenes eutrophus is placed in a suitable medium and fed appropriate nutrients so that it multiplies rapidly.
- PHA synthases are the key enzymes of PHA biosynthesis.
- There are potential applications for PHA produced by micro-organisms within the medical and pharmaceutical industries, primarily due to their biodegradability.

Key Terms

- **Polyhydroxyalkanoates**: Polyhydroxyalkanoates or PHAs are linear polyesters produced in nature by bacterial fermentation of sugar or lipids.
- **fermentation**: Any of many anaerobic biochemical reactions in which an enzyme (or several enzymes produced by a microorganism) catalyses the conversion of one substance into another; especially the conversion (using yeast) of sugars to alcohol or acetic acid with the evolution of carbon dioxide.
- **biodegradability**: The capacity of a material to decompose over time as a result of biological activity, especially to be broken down by microorganisms

Polyhydroxyalkanoates, or PHAs, are linear polyesters produced in nature by bacterial fermentation of sugar or lipids. They are produced by the bacteria to store carbon and energy. More than 150 different monomers can be combined within this family to give materials extremely diverse properties. These plastics are biodegradeable and are used in the production of bioplastics. They can be either thermoplastic or elastomeric materials, with melting points ranging from 40 to 180°C.

The mechanical qualities and biocompatibility of PHA can also be changed by blending, modifying the surface or combining PHA with other polymers, enzymes and inorganic materials, making it possible for a wider range of applications.

PROCESS OF PHA PRODUCTION

To produce PHA, a culture of a micro-organism such as Alcaligenes eutrophus is placed in a suitable medium and fed appropriate nutrients so that it multiplies rapidly. The biosynthesis of PHA is usually caused by certain deficiency conditions (e.g. lack of macro elements such as phosphorus, nitrogen, trace elements, or lack of oxygen) and the excess supply of carbon sources. Recombinants Bacillus subtilis str. pBE2C1 and Bacillus subtilis str. pBE2C1AB were used in production of polyhydroxyalkanoates (PHA) and it was shown that they could use malt waste as carbon source for lower cost of PHA production. As raw material for the fermentation, carbohydrates such as glucose and sucrose can be used, but also vegetable oil or glycerine from biodiesel production. Researchers in the industry are working on methods with which transgenic crops will be developed that express PHA synthesis routes from bacteria and so produce PHA as energy storage in their tissues. Another group of researchers at Micromidas is working to develop methods of producing PHA from municipal waste water. Another even larger scale synthesis can be done with the help of soil organisms. For lack of nitrogen and phosphorus they produce a kilogram of PHA from three kilograms of sugar.

Polyesters are deposited in the form of highly refractive granules in the cells. Depending upon the microorganism and the cultivation conditions, homo- or copolyesters with different hydroxyalkanic acids are generated. PHAs granules are then recovered by disrupting the cells. In the industrial production of PHA, the polyester is extracted and purified from the bacteria by optimizing the conditions of microbial fermentation of sugar or glucose. Once the population has reached a substantial level, the nutrient composition is changed to force the micro-organism to synthesize PHA. The yield of PHA obtained from the intracellular inclusions can be as high as 80% of the organism's dry weight.

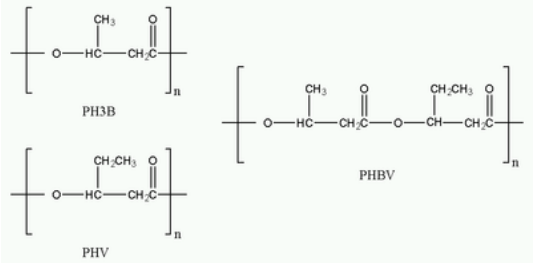

Figure: **Chemical structures of P3HB, PHV and their copolymer PHBV**: Chemical structures of P3HB, PHV and their copolymer PHBV

PHA SYNTHASES

PHA synthases are the key enzymes of PHA biosynthesis. They use the coenzyme A – thioester of (r)-hydroxy fatty acids as substrates. The two classes of PHA synthases differ in the specific use of hydroxyfattyacids of short or medium chain length. The resulting PHA is of the two types: Poly (HA SCL) from hydroxy fatty acids with short chain lengths including three to five carbon atoms are synthesized by numerous bacteria, including Ralstonia eutropha and Alcaligenes latus (PHB). Poly (HA MCL) from hydroxy fatty acids with middle chain lengths including six to 14 carbon atoms, can be made for example, by Pseudomonas putida. A few bacteria, including Aeromonas hydrophila and Thiococcus pfennigii, synthesize copolyester from the above two types of hydroxy fatty acids. The simplest and most commonly occurring form of PHA is the fermentative production of poly-beta-hydroxybutyrate) (poly-3-hydroxybutyrate, P3HB), which consists of 1000 to 30000 hydroxy fatty acid monomers.

PHA APPLICATIONS

PHAs are processed mainly via injection molding, extrusion and extrusion bubbles into films and hollow bodies. A PHA copolymer called PHBV (poly(3-hydroxybutyrate-co-3-hydroxyvalerate)) is less stiff and tougher, and it may be used as packaging material. There are also applications for PHA produced by micro-organisms within the medical and pharmaceutical industries, primarily due to their biodegradability. Some of the fixation and orthopaedic applications that have been devised for these polymers include:

- sutures and suture fasteners
- meniscus repair and regeneration devices
- rivets, tacks, staples, and screws
- bone plates and bone plating systems
- surgical mesh, repair patches, and cardiovascular patches
- vein valves, bone marrow scaffolds
- ligament and tendon grafts
- ocular cell implants
- skin substitutes, bone graft substitutes, and wound dressings

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5.13E: Polyketide Antibiotics

Polyketides are secondary metabolites produced from bacteria, fungi, plants, and animals.

Learning Objectives

- Describe the characteristics associated with polyketides, including: type I, II and III polyketides

Key Points

- Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of an organism.
- Polyketides are usually biosynthesized through the decarboxylative condensation of malonyl-CoA derived extender units in a similar process to fatty acid biosynthesis.
- Polyketides are structurally a very diverse family of natural products with diverse biological activities and pharmacological properties.

Key Terms

- **Polyketides**: Polyketides are secondary metabolites from bacteria, fungi, plants, and animals. Polyketides are usually biosynthesized through the decarboxylative condensation of malonyl-CoA derived extender units in a similar process to fatty acid synthesis (a Claisen condensation).
- **metabolites**: Metabolites are the intermediates and products of metabolism. The term metabolite is usually restricted to small molecules. Metabolites have various functions, including fuel, structure, signaling, stimulatory and inhibitory effects on enzymes, catalytic activity of their own (usually as a cofactor to an enzyme), defense, and interactions with other organisms (e.g. pigments, odorants, and pheromones).
- **biosynthesized**: Biosynthesis (also called biogenesis or “anabolism”) is an enzyme-catalyzed process in cells of living organisms by which substrates are converted to more complex products. The biosynthesis process often consists of several enzymatic steps in which the product of one step is used as substrate in the following step.

Polyketides are secondary metabolites produced from bacteria, fungi, plants, and animals.

Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of an organism. Unlike primary metabolites, the absence of secondary metabolites does not result in immediate death, but rather in long-term impairment of the organism’s survivability, fecundity, or aesthetics, or perhaps in no significant change at all. Secondary metabolites are often restricted to a narrow set of species within a phylogenetic group. Secondary metabolites often play an important role in plant defense against herbivory and other interspecies defenses. Humans use secondary metabolites as medicines, flavorings, and recreational drugs.

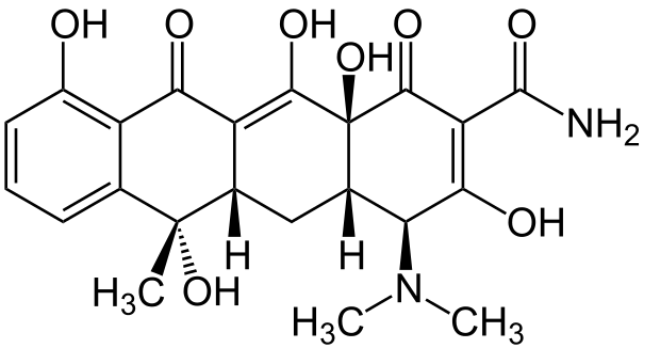

Figure: **Tetracycline structural formula**

Polyketides are usually biosynthesized through the decarboxylative condensation of malonyl-CoA derived extender units in a similar process to fatty acid biosynthesis (a Claisen condensation). The polyketide chains produced by a minimal polyketide synthase are often further derivitized and modified into bioactive natural products.

Polyketides are structurally a very diverse family of natural products with diverse biological activities and pharmacological properties. They are broadly divided into three classes: type I polyketides (often macrolides produced by multimodular megasynthases), type II polyketides (often aromatic molecules produced by the iterative action of dissociated enzymes), and type

III polyketides (often small aromatic molecules produced by fungal species). Polyketide antibiotics, antifungals, cytostatics, anticholesteremic, antiparasitics, coccidiostats, animal growth promoters, and natural insecticides are in commercial use.

Examples of polyketides include: Macrolides; Pikromycin, the first isolated macrolide; the antibiotics erythromycin A; clarithromycin, and azithromycin; the immunosuppressant tacrolimus; Radicicol and Pochonin family (HSP90 inhibitor); Polyene antibiotics; Amphotericin; Tetracyclines and the tetracycline family of antibiotics.

Polyketides are synthesized by one or more specialized and highly complex polyketide synthase (PKS) enzymes.

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SECTION OVERVIEW

5.14: Amino Acids and Nucleotide Biosynthesis

Topic hierarchy

5.14A: Amino Acid Synthesis

5.14B: Purine and Pyrimidine Synthesis

5.14C: Nonribosomal Peptide Antibiotics

5.14D: Biosynthesis of Tetrapyrroles

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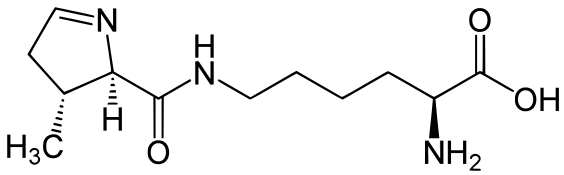
5.14A: Amino Acid Synthesis

Learning Objectives

- Recognize the factors involved in amino acid synthesis

Amino acids are the structural units that make up proteins. They join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighboring amino acids. The process of making proteins is called translation and involves the step-by-step addition of amino acids to a growing protein chain by a ribozyme that is called a ribosome. The order in which the amino acids are added is read through the genetic code from an mRNA template, which is a RNA copy of one of the organism ‘s genes.

Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or natural amino acids. Of these, 20 are encoded by the universal genetic code. The remaining two, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms. Selenocysteine is incorporated when the mRNA being translated includes a SECIS element, which causes the UGA codon to encode selenocysteine instead of a stop codon. Pyrrolysine is used by some methanogenic archaea in enzymes that they use to produce methane. It is coded with the codon UAG, which is normally a stop codon in other organisms. Pyrrolysine (abbreviated as Pyl or O) is a naturally occurring amino acid similar to lysine, but with an added pyrroline ring linked to the end of the lysine side chain. Produced by a specific tRNA and aminoacyl tRNA synthetase, it forms part of an unusual genetic code in these organisms. It is considered the 22nd proteinogenic amino acid. This UAG codon is followed by a PYLIS downstream sequence.



Structure of Pyrrolysine: Pyrrolysine (abbreviated as Pyl or O) is a naturally occurring, genetically coded amino acid used by some methanogenic archaea and one known bacterium in enzymes that are part of their methane-producing metabolism.

Organisms vary in their ability to synthesize the 20 common amino acids. Most bacteria and plants can synthesize all 20. Some simple parasites, such as the bacteria *Mycoplasma pneumoniae*, lack all amino acid synthesis and take their amino acids directly from their hosts. All amino acids are synthesized from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway. Nitrogen is provided by glutamate and glutamine. Amino acid synthesis depends on the formation of the appropriate alpha-keto acid, which is then transaminated to form an amino acid. Amino acids are made into proteins by being joined together in a chain by peptide bonds. Each different protein has a unique sequence of amino acid residues: this is its primary structure. Just as the letters of the alphabet can be combined to form an almost endless variety of words, amino acids can be linked in varying sequences to form a huge variety of proteins. Proteins are made from amino acids that have been activated by attachment to a transfer RNA molecule through an ester bond.

Aside from the 22 standard amino acids, there are many other amino acids that are called non-proteinogenic or non-standard. Those either are not found in proteins (for example carnitine, GABA) or are not produced directly and in isolation by standard cellular machinery (for example, hydroxyproline and selenomethionine). Non-standard amino acids that are found in proteins are formed by post-translational modification, which is modification after translation during protein synthesis. These modifications are often essential for the function or regulation of a protein. For example, the carboxylation of glutamate allows for better binding of calcium cations. The hydroxylation of proline is critical for maintaining connective tissues. Another example is the formation of hypusine in the translation initiation factor EIF5A, through modification of a lysine residue. Such modifications can also determine the localization of the protein, e.g., the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane. Some nonstandard amino acids are not found in proteins. Examples include lanthionine, 2-aminoisobutyric acid, dehydroalanine, and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids — for example, ornithine and citrulline occur in the urea cycle, part of amino acid catabolism.

Key Points

- All amino acids are synthesized from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway.
- Amino acid synthesis depends on the formation of the appropriate alpha-keto acid, which is then transaminated to form an amino acid.
- Of the 22 amino acids naturally incorporated into proteins, 20 are encoded by the universal genetic code and the remaining two, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms.

Key Terms

- **pyrrolysine**: An amino acid found in methanogenic bacteria.
- **selenocysteine**: A naturally-occurring amino acid, present in several enzymes, whose structure is that of cysteine but with the sulfur atom replaced by one of selenium.
- **genetic code**: The set of rules by which the sequence of bases in DNA are translated into the amino acid sequence of proteins

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5.14B: Purine and Pyrimidine Synthesis

Organisms vary in their ability to synthesize the 20 common amino acids, but most bacteria and plants can synthesize all 20.

Learning Objectives

- Recognize the factors involved in amino acid synthesis

Key Points

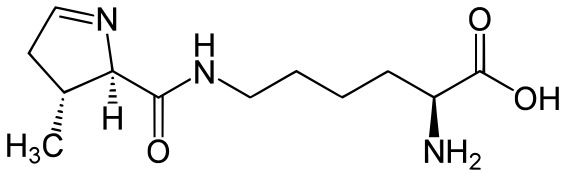
- All amino acids are synthesized from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway.
- Amino acid synthesis depends on the formation of the appropriate alpha-keto acid, which is then transaminated to form an amino acid.
- Of the 22 amino acids naturally incorporated into proteins, 20 are encoded by the universal genetic code and the remaining two, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms.

Key Terms

- **pyrrolysine**: An amino acid found in methanogenic bacteria.
- **selenocysteine**: A naturally-occurring amino acid, present in several enzymes, whose structure is that of cysteine but with the sulfur atom replaced by one of selenium.
- **genetic code**: The set of rules by which the sequence of bases in DNA are translated into the amino acid sequence of proteins

Amino acids are the structural units that make up proteins. They join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighboring amino acids. The process of making proteins is called translation and involves the step-by-step addition of amino acids to a growing protein chain by a ribozyme that is called a ribosome. The order in which the amino acids are added is read through the genetic code from an mRNA template, which is a RNA copy of one of the organism ‘s genes.

Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or natural amino acids. Of these, 20 are encoded by the universal genetic code. The remaining two, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms. Selenocysteine is incorporated when the mRNA being translated includes a SECIS element, which causes the UGA codon to encode selenocysteine instead of a stop codon. Pyrrolysine is used by some methanogenic archaea in enzymes that they use to produce methane. It is coded with the codon UAG, which is normally a stop codon in other organisms. Pyrrolysine (abbreviated as Pyl or O) is a naturally occurring amino acid similar to lysine, but with an added pyrroline ring linked to the end of the lysine side chain. Produced by a specific tRNA and aminoacyl tRNA synthetase, it forms part of an unusual genetic code in these organisms. It is considered the 22nd proteinogenic amino acid. This UAG codon is followed by a PYLIS downstream sequence.



Structure of Pyrrolysine: Pyrrolysine (abbreviated as Pyl or O) is a naturally occurring, genetically coded amino acid used by some methanogenic archaea and one known bacterium in enzymes that are part of their methane-producing metabolism.

Organisms vary in their ability to synthesize the 20 common amino acids. Most bacteria and plants can synthesize all 20. Some simple parasites, such as the bacteria Mycoplasma pneumoniae, lack all amino acid synthesis and take their amino acids directly from their hosts. All amino acids are synthesized from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway. Nitrogen is provided by glutamate and glutamine. Amino acid synthesis depends on the formation of the appropriate alpha-keto acid, which is then transaminated to form an amino acid. Amino acids are made into proteins by being joined together in a chain by peptide bonds. Each different protein has a unique sequence of amino acid residues: this is its primary structure. Just as the letters of the alphabet can be combined to form an almost endless variety of words, amino acids can be linked in varying sequences to form a huge variety of proteins. Proteins are made from amino acids that have been activated by attachment to a transfer RNA molecule through an ester bond.

Aside from the 22 standard amino acids, there are many other amino acids that are called non-proteinogenic or non-standard. Those either are not found in proteins (for example carnitine, GABA) or are not produced directly and in isolation by standard cellular machinery (for example, hydroxyproline and selenomethionine). Non-standard amino acids that are found in proteins are formed by post-translational modification, which is modification after translation during protein synthesis. These modifications are often essential for the function or regulation of a protein. For example, the carboxylation of glutamate allows for better binding of calcium cations. The hydroxylation of proline is critical for maintaining connective tissues. Another example is the formation of hypusine in the translation initiation factor EIF5A, through modification of a lysine residue. Such modifications can also determine the localization of the protein, e.g., the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane. Some nonstandard amino acids are not found in proteins. Examples include lanthionine, 2-aminoisobutyric acid, dehydroalanine, and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids — for example, ornithine and citrulline occur in the urea cycle, part of amino acid catabolism.

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5.14C: Nonribosomal Peptide Antibiotics

Nonribosomal peptides (NRP) are a class of peptide secondary metabolites which can function as antibiotics.

Learning Objectives

- Outline the characteristics associated with nonribosomal peptides and the production of antibiotics

Key Points

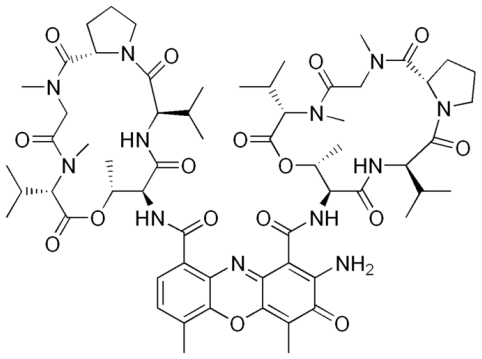
- Nonribosomal peptides are produced by microorganisms like bacteria and fungi but are also found in higher organisms such as nudibranchs where they are thought to be made by bacteria inside these organisms.
- Nonribosomal peptides are synthesized by nonribosomal peptide synthetases, which, unlike the ribosomes, are independent of messenger RNA.
- The biosynthesis of nonribosomal peptides shares characteristics with the polyketide and fatty acid biosynthesis.

Key Terms

- **peptide**: A class of organic compounds consisting of various numbers of amino acids, in which the amine of one is reacted with the carboxylic acid of the next to form an amide bond.
- **metabolite**: Any substance produced by, or taking part in, a metabolic reaction.
- **siderophores**: Sidereophores are small, high-affinity iron chelating compounds secreted by microorganisms such as bacteria and fungi, and also grasses. Siderophores are amongst the strongest soluble Fe3+ binding agents known.

Nonribosomal peptides (NRP) are a class of peptide secondary metabolites, usually produced by microorganisms like bacteria and fungi. Nonribosomal peptides are also found in higher organisms (such as nudibranchs) but are thought to be made by bacteria inside these organisms. While there exists a wide range of peptides that are not synthesized by ribosomes, the term nonribosomal peptide typically refers to a very specific set of these as discussed in this article.

Nonribosomal peptides are synthesized by nonribosomal peptide synthetases, which, unlike the ribosomes, are independent of messenger RNA. Each nonribosomal peptide synthetase can synthesize only one type of peptide. Nonribosomal peptides often have a cyclic and/or branched structures, can contain non-proteinogenic amino acids including D-amino acids, carry modifications like N-methyl and N-formyl groups, or are glycosylated, acylated, halogenated, or hydroxylated. Cyclization of amino acids against the peptide “backbone” is often performed, resulting in oxazolines and thiazolines; these can be further oxidized or reduced. On occasion, dehydration is performed on serines, resulting in dehydroalanine. This is just a sampling of the various manipulations and variations that nonribosomal peptides can perform. Nonribosomal peptides are often dimers or trimers of identical sequences chained together or cyclized, or even branched.



Actinomycin D: Actinomycin D (also known generically as Actinomycin or Dactinomycin), is the most significant member of actinomycines, which are a class of polypeptide antibiotics isolated from soil bacteria of the genus Streptomyces. As one of the older chemotherapy drugs, it has been used for many years.

Nonribosomal peptides are a very diverse family of natural products with an extremely broad range of biological activities and pharmacological properties. They are often toxins, siderophores, or pigments. Nonribosomal peptide antibiotics (for example, actinomycin D), cytostatics, and immunosuppressants are used commercially.

Nonribosomal peptides are synthesized by one or more specialized nonribosomal peptide-synthetase (NRPS) enzymes. The NRPS genes for a certain peptide are usually organized in one operon in bacteria and in gene clusters in eukaryotes. However the first fungal NRP to be found was ciclosporin. It is synthesized by a single 1.6MDa NRPS. The enzymes are organized in modules that are responsible for the introduction of one additional amino acid. Each module consists of several domains with defined functions, separated by short spacer regions of about 15 amino acids.

The biosynthesis of nonribosomal peptides shares characteristics with the polyketide and fatty acid biosynthesis. Due to these structural and mechanistic similarities, some nonribosomal peptide synthetases contain polyketide synthase modules for the insertion of acetate or propionate-derived subunits into the peptide chain.

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5.14D: Biosynthesis of Tetrapyrroles

Porphyrins are the conjugate acids of ligands that bind metals to form complexes.

Learning Objectives

- Recall the process of tetrapyrrole biosynthesis

Key Points

- Porphyrins are a group of organic compounds, many naturally occurring, such as heme.
- Porphyrins are aromatic, obeying Hückel's rule for aromaticity, possessing 4n+2 π electrons (n=4 for the shortest cyclic path) delocalized over the macrocycle.
- Porphyrin macrocycles are highly conjugated systems and typically have very intense absorption bands in the visible region, and may be deeply colored.

Key Terms

- **heterocyclic**: Having one or more atoms other than carbon in at least one of its rings.
- **porphyrin**: Any of a class of heterocyclic compounds containing four pyrrole rings arranged in a square; they are important in biochemistry in a form with a metal atom in the central cavity (hemoglobin with iron, chlorophyll with magnesium, etc.).
- **aromatic**: Having a closed ring of alternate single and double bonds with delocalized electrons.

Porphyrins are a group of organic compounds, many naturally occurring. One of the best-known porphyrins is heme, the pigment in red blood cells. Heme is a cofactor of the protein hemoglobin. The main "application" of porphyrins is their role in supporting aerobic life. For example, complexes of meso-tetraphenylporphyrin, e.g., the iron(III) chloride complex (TPPFeCl), catalyze a variety of reactions of potential interest in organic synthesis.

Porphyrins are heterocyclic macrocycles composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH-). Porphyrins are aromatic, obeying Hückel's rule for aromaticity, possessing 4n+2 π electrons (n=4 for the shortest cyclic path) delocalized over the macrocycle. Thus, porphyrin macrocycles are highly conjugated systems. As a consequence, they typically have very intense absorption bands in the visible region and may be deeply colored. (The name porphyrin comes from a Greek word for purple.) The macrocycle has 26 pi electrons in total. The parent porphyrin is porphine, and substituted porphines are called porphyrins.

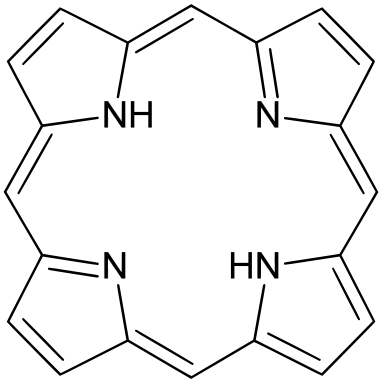

Figure: **Structure of Porphine**: Porphine is the simplest porphyrin, an aromatic organic compound.

Porphyrins are the conjugate acids of ligands that bind metals to form complexes. The metal ion usually has a charge of 2+ or 3+. A schematic equation for these syntheses is:

H_2porphyrin + [MLn]2+ → M(porphyrinate)Ln-4 + 4 L + 2 H+

where M=metal ion and L=a ligand

A porphyrin without a metal ion in its cavity is a free base. Some iron-containing porphyrins are called hemes. Heme-containing proteins, or hemoproteins, are found extensively in nature. Hemoglobin and myoglobin are two O2-binding proteins that contain iron porphyrins. Various cytochromes are also hemoproteins. Several other heterocycles are related to porphyrins. These include corrins, chlorins, bacteriochlorophylls and corphins. Chlorins (2,3-dihydroporphyrin) are more reduced, contain more hydrogen

than porphyrins, and feature a pyrroline subunit. This structure occurs in a chlorophyll molecule. Replacement of two of the four pyrrolic subunits with pyrrolinic subunits results in either a bacteriochlorin (as found in some photosynthetic bacteria) or an isobacteriochlorin, depending on the relative positions of the reduced rings. Some porphyrin derivatives follow Hückel's rule, but most do not.

The "committed step" for porphyrin biosynthesis is the formation of δ-aminolevulinic acid (δ-ALA, 5-ALA or dALA) by the reaction of the amino acid glycine with succinyl-CoA from the citric acid cycle. Two molecules of dALA combine to give porphobilinogen (PBG), which contains a pyrrole ring. Four PBGs are then combined through deamination into hydroxymethyl bilane (HMB), which is hydrolysed to form the circular tetrapyrrole uroporphyrinogen III. This molecule undergoes a number of further modifications. Intermediates are used in different species to form particular substances, but, in humans, the main end-product protoporphyrin IX is combined with iron to form heme. Bile pigments are the breakdown products of heme.

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SECTION OVERVIEW

5.15: Nitrogen Fixation

Topic hierarchy

5.15A: Nitrogenase and Nitrogen Fixation

5.15B: Early Discoveries in Nitrogen Fixation

5.15C: Nitrogen Fixation Mechanism

5.15D: Anaerobiosis and N_2 Fixation

5.15E: Genetics and Regulation of N_2 Fixation

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5.15A: Nitrogenase and Nitrogen Fixation

Learning Objectives

- Describe the importance of nitrogen fixation

Nitrogen fixation also refers to other biological conversions of nitrogen, such as its conversion to nitrogen dioxide. Nitrogen fixation is a process by which nitrogen (N_2) in the atmosphere is converted into ammonia (NH_3). Atmospheric nitrogen or elemental nitrogen (N_2) is relatively inert: it does not easily react with other chemicals to form new compounds. Dinitrogen is quite inert because of the strength of its N≡N triple bond. To break one nitrogen atom away from another requires breaking all three of these chemical bonds. Fixation processes free up the nitrogen atoms from their diatomic form (N_2) to be used in other ways. Nitrogen fixation, natural and synthetic, is essential for all forms of life because nitrogen is required to biosynthesize basic building blocks of plants, animals, and other life forms, e.g., nucleotides for DNA and RNA and amino acids for proteins. Therefore, nitrogen fixation is essential for agriculture and the manufacture of fertilizer. Microorganisms that fix nitrogen are bacteria called diazotrophs.

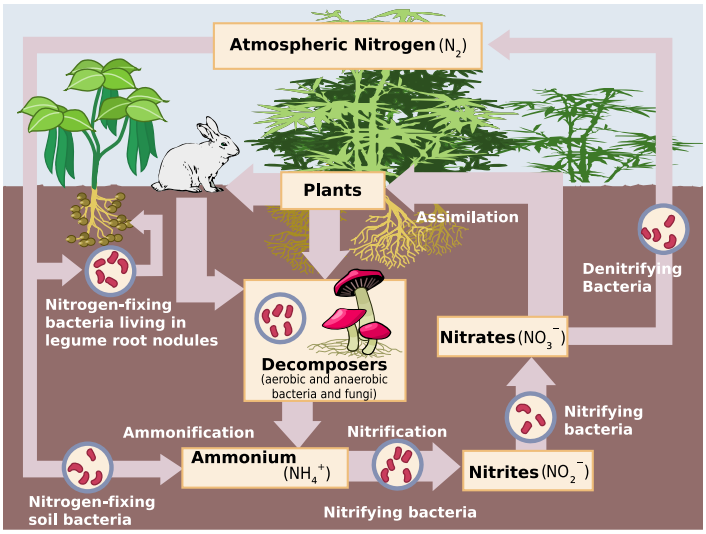

Figure: **The role of soil bacteria in the Nitrogen cycle**: Nitrogen transitions between various biologically useful forms.

Some higher plants, and some animals (termites), have formed associations (symbioses) with diazotrophs. Diazotrophs are microbes. They are intensively studied by microbiologists. Biological nitrogen fixation was discovered by the German agronomist Hermann Hellriegel and Dutch microbiologist Martinus Beijerinck. Biological nitrogen fixation (BNF) occurs when atmospheric nitrogen is converted to ammonia by an enzyme called nitrogenase. Nitrogenases are enzymes used by some organisms to fix atmospheric nitrogen gas (N_2). There is only one known family of enzymes that accomplishes this process. All nitrogenases have an iron – and sulfur-containing cofactor that includes a heterometal complex in the active site (e.g., FeMoCo). In most species, this heterometal complex has a central molybdenum atom. However, in some species it is replaced by a vanadium or iron atom. Enzymes responsible for nitrogenase action are very susceptible to destruction by oxygen. Many bacteria cease production of the enzyme in the presence of oxygen. Many nitrogen-fixing organisms exist only in anaerobic conditions, respiring to draw down oxygen levels, or binding the oxygen with proteins.

Key Points

- Nitrogen fixation takes elemental nitrogen (N_2) and converts it into a ammonia, a format usable by biological organism.
- The fixed form of nitrogen (NH_3) is needed as an essential component of DNA and proteins. Therefore, it is needed for all life on earth.
- Nitrogen fixation is carried out by the enzyme nitrogenase, which are found in microbes.

Key Terms

- **fixation**: The act of uniting chemically with a solid substance or in a solid form; reduction to a non-volatile condition; — said of gaseous elements.

- **cofactor**: A substance, especially a coenzyme or a metal, that must be present for an enzyme to function.
- **heterometal**: Describing a complex containing two (or more) different metals
- **nitrogen fixation**: the conversion of atmospheric nitrogen into ammonia and organic derivatives, by natural means, especially such conversion, by microorganisms in the soil, into a form that can be assimilated by plants

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5.15B: Early Discoveries in Nitrogen Fixation

Learning Objectives

- Outline the early discoveries of nitrogen fixation

For thousands of years farmers were aware that plants belonging to the legume family, such as peas and soy beans, promoted crop growth when planted with other non-legumes such as wheat. Growing a legume crop in a field could also result in the next year's crop of non-legume plants giving a far greater yield. This led to the practice of crop rotation, a practice which can be traced back to techniques recorded in Roman literature.

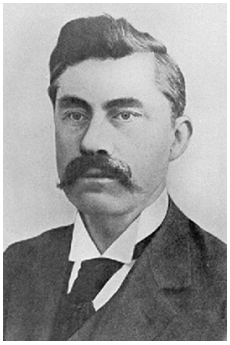

Figure: ***Martinus Beijerinck****: Work done by Martinus Beijerinck was key to the discovery of rhizobia, symbiotic bacteria found on the roots of legumes and responsible for nitrogen fixation.*

While the ancient Romans were aware of the improved results gained through crop rotation, they did not know that these benefits were brought about through the replenishment of nitrogen in the soil. Later people knew legumes did replenish nitrogen in the soil, but did not know how atmospheric (N_2) was converted into ammonium (NH_3) by legumes until research done in the 19thcentury. Hermann Hellriegel (1831-1895), a noted German agricultural chemist, discovered that leguminous plants took atmospheric nitrogen and replenished the ammonium in the soil through the process now known as nitrogen fixation. He found that the nodules on the roots of legumes are the location where nitrogen fixation takes place.

HELLRIEGEL'S AND BEIJERINCK'S DISCOVERIES

Hellriegel did not determine what factors in the root nodules carried out nitrogen fixation. Martinus Willem Beijerinck (March 16, 1851 – January 1, 1931), a Dutch microbiologist and botanist, explored the mechanism responsible, discovering that the root nodules contained microbes. He further demonstrated that these microbes were bacteria, which he named rhizobia. These rhizobia perform the chemical processes of nitrogen fixation. In addition to having discovered this biochemical reaction vital to soil fertility and agriculture, Beijerinck is responsible for the discovery of this classic example of symbiosis between plants and bacteria. The bacteria in the root nodules are needed to provide nitrogen for legume growth, while the rhizobia are dependent on the root nodules as a environment to grow.and a source of nutrition.

Key Points

- A key benefit of crop rotation is the introduction of nitrogen into the soil. Although farmers have used this technique for millennia, it wasn't until the 19th century scientists determined how this fertilization occurred.
- Nitrogen fixation occurs in root nodules of plants belonging to the legume family.
- The root nodules of legumes contain symbiotic bacteria which contain the enzymes needed for nitrogen fixation.

Key Terms

- **legume**: Any of a large family (Leguminosae syn. Fabaceae) of dicotyledonous herbs, shrubs, and trees having fruits that are legumes or loments, bearing nodules on the roots that contain nitrogen-fixing bacteria, and including important food and forage plants (as peas, beans, or clovers).
- **symbiosis**: A close, prolonged association between two or more organisms of different species, regardless of benefit to the members.

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5.15C: Nitrogen Fixation Mechanism

Learning Objectives

- Distinguish between component I and II of the nitrogenase enzyme and its role in biological nitrogen fixation

Biological nitrogen fixation (BNF) occurs when atmospheric nitrogen is converted to ammonia by an enzyme called nitrogenase. The reaction for BNF is:

$$N_2 + 8\,H^+ + 8\,e^- \rightarrow 2\,NH_3 + H_2. \tag{5.15C.1}$$

This type of reaction results in N_2 gaining electrons (see above equation) and is thus termed a reduction reaction. The exact mechanism of catalysis is unknown due to the technical difficulties biochemists have in actually visualizing this reaction in vitro, so the exact sequence of the steps of this reaction are not completely understood. Despite this, a great deal is known of the process. While the equilibrium formation of ammonia from molecular hydrogen and nitrogen has an overall negative enthalpy of reaction (i.e. it gives off energy), the energy barrier to activation is very high without the assistance of catalysis, which is done by nitrogenases. The enzymatic reduction of N_2 to ammonia therefore requires an input of chemical energy, released from ATP hydrolysis, to overcome the activation energy barrier.

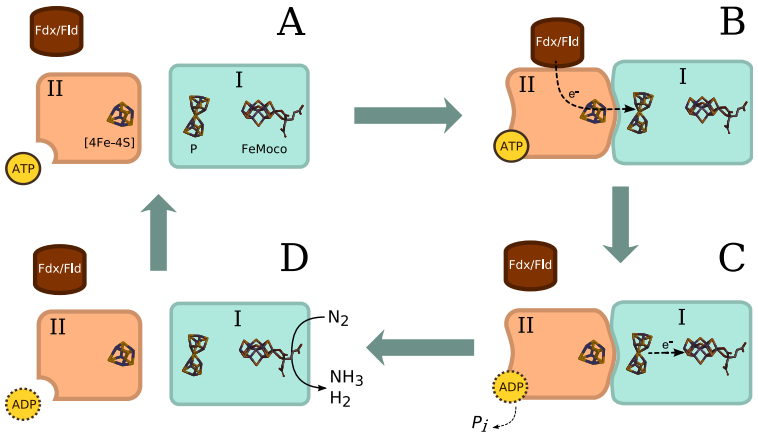

Figure: ***A General Catalytic Mechanism Scheme for Nitrogenase****: A) Components I and II are dissociated; II is ready for reduction. B) ATP binds to component II, which receives electrons from an electron donor (ferredoxin or flavodoxin); binding of ATP induces an allosteric conformational change which allows association of the two proteins. Electrons flow from the [4Fe-4S] cluster on II to the P cluster on I. C) Electrons are further shuttled to the iron-molybdenum cofactor (FeMoco), and ATP is hydrolised to ADP. This step is repeated several times before a molecule of N2 can bind to FeMoco. D) The protein complex dissociates, and nitrogenase reduces dinitrogen to ammonia and dihydrogen. Legend:I: component I (dinitrogenase; MoFe protein); II: component II (dinitrogen reductase; Fe protein); ATP: adenosine triphosphate; ADP: adenosine diphosphate; Fdx: ferredoxin; Fld: flavodoxin.*

Nitrogenase is made up of two soluble proteins: component I and II. Component I known as MoFe protein or nitrogenase contains 2 Mo atoms, 28 to 34 Fe atoms, and 26 to 28 acid-labile sulfides, also known as a iron-molybdenum cofactor (FeMoco). Component I is composed of two copies each of two subunits (α and β); each subunit's stability depends on the other in vivo. Component II known as Fe protein or nitrogenase reductase is composed of two copies of a single subunit. This protein has four non-heme Fe atoms and four acid-labile sulfides (4Fe-4S). Substrate binding and reduction takes place on component I, which binds to ATP and ferredoxin or flavodoxin proteins (Fdx or Fld) (see step B).

The hydrolysis of ATP supplies the energy for the reaction while the Fdx/Fld proteins supply the electrons. Note this is a reduction reaction which means that electrons must be added to the N_2 to reduce it to NH_4. Thus, the role of component II is to supply electrons, one at a time to component I. ATP is not hydrolyzed to ADP until component II transfers an electron to component I (see step C and D). 21-25 ATPs are required for each N_2 fixed. The association of nitrogenase component I and II and later dissociation occurs several times to allow the fixation of one N_2 molecule (see step B and D).

Nitrogenase ultimately bonds each atom of nitrogen to three hydrogen atoms to form ammonia (NH_3). The nitrogenase reaction additionally produces molecular hydrogen as a side product, which is of special interest for people trying to produce H_2 as an alternative energy source to fossil fuels.

Key Points

- Nitrogen fixation does result in the release of energy, but the activation of this reaction takes energy in the form of ATP hydrolysis.
- Nitrogenases are metalloenzymes, which are proteins that have metalic molecules as subunits.
- While a great deal is known about how nitrogenases reduce nitrogen, some steps are unknown.

Key Terms

- **sulfide**: Any compound of sulfur and a metal or other electropositive element or group.
- **reduction**: A reaction in which electrons are gained and valence is reduced; often by the removal of oxygen or the addition of hydrogen.
- **enthalpy**: In thermodynamics, a measure of the heat content of a chemical or physical system.

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5.15D: Anaerobiosis and N_2 Fixation

Learning Objectives

- Outline the various mechanisms utilized by nitrogen-fixing bacteria to protect nitrogenases from oxygen

Central to nitrogen fixation (N_2 to NH_3) are the enzymes that do the actual fixation, these are known as nitrogenases. Due to the oxidation carried out by oxygen, most nitrogenases, which are essential large reduction complexes are irreversibly inhibited by O_2, which degradatively oxidizes the Fe-S cofactors. In essence, O_2binds to the iron (Fe) found in nitrogenases and blocks their ability to bind to N_2. To protect nitrogenases, there are mechanisms for nitrogen fixers to protect nitrogenase from oxygen in vivo. One known exception is the nitrogenase of Streptomyces thermoautotrophicus, which is unaffected by the presence of oxygen. This is complicated by the fact the bacteria still need the presence of oxygen for proper respiration.

Some microbes have a proteoglycan rich extra cellular matrix which traps a layer of water, often referred to as a slime layer. This slime layer acts as a barrier for oxygen. The ability of some nitrogen fixers such as azotobacteraceae to employ an oxygen-amendable nitrogenase under aerobic conditions has been attributed to a high metabolic rate, allowing oxygen reduction at the cell membrane; however, the effectiveness of this mechanism is in question.

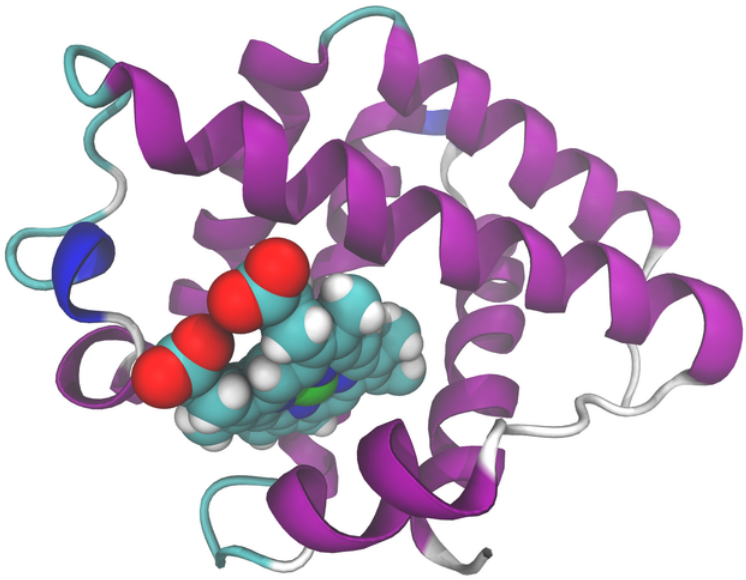

Figure: ***Leghemoglobin****: Leghemoglobin, the protein which binds to oxygen, allowing nitrogenases to function in an oxygen free environment. The ribbons represent protein folds, while the conglomerate of spheres are the postion of the iron contain heme group which binds the oxygen.*

Many rhizobia, nitrogen fixing bacteria, live in a symbiotic relationship with plants known as legumes. They have an interesting strategy to deal with O_2. In plants infected with Rhizobium, (legumes such as alfalfa or soybeans), the presence of oxygen in the root nodules would reduce the activity of the oxygen-sensitive nitrogenase. In these situations, the roots of such plants produce a protein known as leghemoglobin (also leghaemoglobin or legoglobin). Leghemoglobin buffers the concentration of free oxygen in the cytoplasm of infected plant cells to ensure the proper function of root nodules. Leghemoglobin is a nitrogen or oxygen carrier; naturally occurring oxygen and nitrogen interact similarly with this protein. Leghemoglobin buffers the concentration of free oxygen in the cytoplasm of infected plant cells to ensure the proper function of root nodules. It has close chemical and structural similarities to hemoglobin, and, like hemoglobin, is red in colour. Leghemoglobin has a high affinity for oxygen, about ten times higher than of human hemoglobin. This allows an oxygen concentration that is low enough to allow nitrogenase to function but not so high as to bind all the O_2 in the bacteria, providing the bacteria with oxygen for respiration.

Leghemoglobin is produced by legumes in response to the roots being infected by rhizobia, as part of the symbiotic interaction between the plant and these nitrogen-fixing bacterium. Interestingly, it is widely believed that leghemoglobin is the product of both the plant and the bacterium in which a protein precursor is produced by the plant and the heme (an iron atom bound in a porphyrin

ring, which binds O_2) is produced by the bacterium. The protein and heme come together to function, allowing the bacteria to fix-nitrogen, giving the plant usable nitrogen and thus the plant provides the rhizobia a home.

Key Points

- The iron (Fe) found in nitrogenases is very sensitive to oxygen, if there is too much oxygen this will in the end disrupt nitrogenase function.
- Some bacteria produce barriers which protect themselves from oxygen, while others use proteins such as leghemoglobin to bind up oxygen which may interfere with nitrogenases.
- Portions of leghemoglobin are thought to be produced by rhizobia residing in plant nodules, while other parts are produced by the plant, an elegant example of symbiosis.

Key Terms

- **oxidation**: A reaction in which the atoms of an element lose electrons and the valence of the element increases.
- **reduction**: A reaction in which electrons are gained and valence is reduced; often by the removal of oxygen or the addition of hydrogen.
- **proteoglycan**: Any of many glycoproteins that have heteropolysaccharide side chains

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5.15E: Genetics and Regulation of N_2 Fixation

Learning Objectives

- Discuss the role of the nif genes in controlling nitrogen fixation

The fixation of atmospheric nitrogen (N_2) is a very energy intensive endeavor. If there is no need for N_2 fixation, the production of proteins needed for fixation are tightly controlled. The nif genes are responsible for the coding of proteins related and associated with the fixation of atmospheric nitrogen into a form of nitrogen available to plants. These genes are found in nitrogen fixing bacteria and cyanobacteria. The nif genes are found in both free living nitrogen fixing bacteria and in symbiotic bacteria in various plants.

The nif genes are genes encoding enzymes involved in the fixation of atmospheric nitrogen. The primary enzyme encoded by the nif genes is the nitrogenase complex which is in charge of converting atmospheric nitrogen to other nitrogen forms such as ammonia, which plants can use for various purposes. Besides the nitrogenase enzyme, the nif genes also encode a number of regulatory proteins involved in nitrogen fixation. The expression of the nif genes is induced as a response to low concentrations of fixed nitrogen and oxygen concentrations (the low oxygen concentrations are actively maintained in the root environment). Nitrogen fixation is regulated by nif regulon, which is a set of seven operons which includes 17 nif genes. Nif genes have both positive and negative regulators. Some of nif genes are: Nif A, D, L,K, F,H S,U,Y,W,Z.

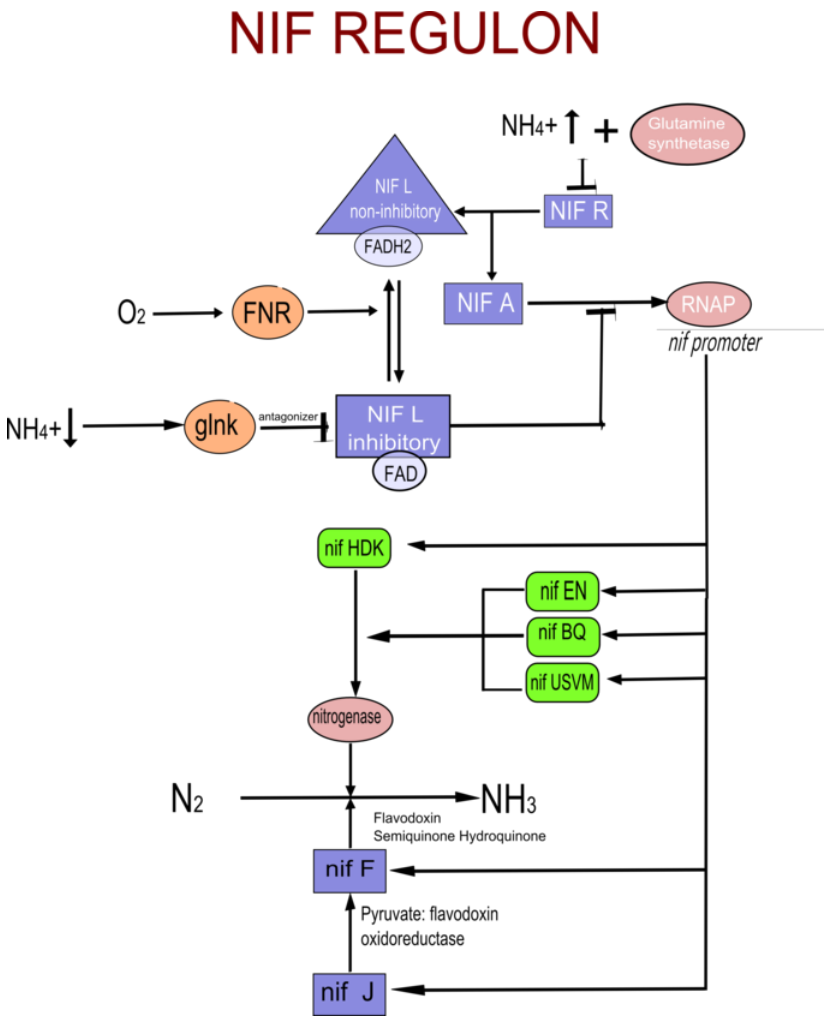

Figure: ***Nif Regulon***: *This is a schematic representing many of the proteins in the nif regulon and where they act in the pathway needed for nitrogen fixation.*

Activation of nif genes transcription is done by the nitrogen sensitive NifA protein. When there isn't enough fixed nitrogen factor available for the plant's use, NtrC, which is a RNA polymerase, triggers NifA's expression. NifA then activates the rest of the

transcription for the nif genes. If there is a sufficient amount of reduced nitrogen or oxygen is present, another protein is activated, NifL. In turn, NifL inhibits NifA activity, which results in the inhibition of nitrogenase formation. NifL is then regulated by other proteins that are sensors for the levels of O_2 and ammonium in the surrounding environment.

The nif genes can be found on bacteria's chromosomes, but many times they are found on bacteria's plasmids with other genes related to nitrogen fixation, such as the genes needed for the bacteria to communicate with the plant host.

Key Points

- Nitrogen fixation takes a great deal of energy. If the conditions are not favorable for nitrogen fixation or there is enough ammonia around, nitrogen-fixing bacteria turn off the production of proteins needed for nitrogen fixation.
- Nitrogen fixing protein production is regulated by the nif regulon.
- The nif regulon contains factors which both turn on and off the production of proteins needed for nitrogen-fixation.

Key Terms

- **regulon**: A group of genes that is regulated by the same regulatory molecule. The genes of a regulon share a common regulatory element binding site or promoter. The genes comprising a regulon may be located non-contiguously in the genome.
- **operon**: A unit of genetic material that functions in a coordinated manner by means of an operator, a promoter, and structural genes that are transcribed together.

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6.1C: Limitation of Microbial Growth by Nutrient Supply

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Thumbnail: A Petri dish with bacterial colonies on an agar-based growth medium. (Public Domain; U.S. National Oceanic and Atmospheric Administration).

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SECTION OVERVIEW

6.1: Microbial Nutrition

Topic hierarchy

6.1A: Chemical Analysis of Microbial Cytoplasm

6.1B: Sources of Essential Nutrients

6.1C: Limitation of Microbial Growth by Nutrient Supply

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6.1A: Chemical Analysis of Microbial Cytoplasm

Learning Objectives

- Describe the ultrastructure of the microbial cytoplasm

The bacterial cytoplasmic membrane plays a role in permeability and energy conservation in microbial cell structure. The cytoplasmic membranes in bacteria are composed of a phospholipid bilayer; this layer differs from those found in eukaryotes in their lack of sterols. The membranes however, may contain compounds called hopanoids and various fatty acids as well.

The fatty acids present within the cytoplasmic membrane are categorized into classes based on the addition of functional groups; methyl or hydroxyl groups are two examples of such groups. The cytoplasm itself is enclosed within the membrane. In bacteria it lacks the structures seen in eukaryotic cells, including a mitochondria, nucleus, or chloroplasts. The components of the microbial cytoplasm include macromolecules, smaller molecules, various inorganic ions, and cytoplasmic inclusions. The macromolecules included in a bacterial cytoplasm include proteins, DNA, RNA molecules. Smaller molecules include precursors to macromolecules and vitamins. Below is an overview of the components found in microbial cytoplasm based on chemical analysis.

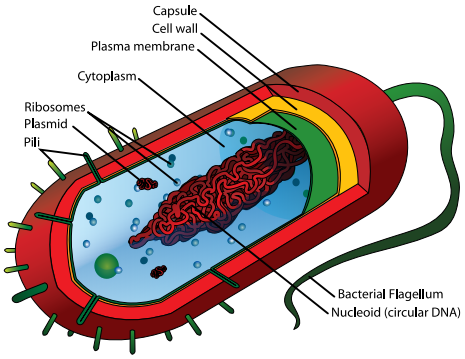

Figure: ***Typical Prokaryotic Cell****: Structure of a typical prokaryotic cell. Note the location of the cytoplasm and its components.*

The cytosol is a major component of the cytoplasm; it is the liquid portion of the cytoplasm that is not enclosed within a membrane-bound component. The cytosol is typically composed of water, salts, and organic molecules. Elements found within the cytosol include carbon, hydrogen, nitrogen, oxygen, phosphorous, and sulfur. These elements are critical to metabolic processes used by microbes.

Macromolecules found within bacterial cytoplasm include the nucleoid region, ribosomes, proteins, and enzymes. The nucleoid region is the area within the cell that houses the genetic material. Prokaryotes may sometimes contain an extra chromosomal piece of DNA referred to as the plasmid. The ribosomes, similar to ribosomes in eukaryotes, are responsible for protein synthesis. Unlike eukaryotes, prokaryotes, specifically bacteria, typically contain one cytosol-specific ribosome. Eukaryotes have multiple types of ribosomes, including the mitochondria and cytosol).

Another group of substances found within the cytoplasm include small particles referred to as inclusions. These inclusions are characterized by their granular appearance and insolubility. They are suspended in the cytosol. Inclusions vary, based on cell types. Typically, inclusions function as reserve materials. In prokaryotes, for example, lipid droplets are plentiful in cells which require lipid storage mechanisms. These lipid droplets store molecules such as fatty acids which are present in the cytoplasmic membrane of prokaryotes. *E. coli* offers another example of bacterial inclusions. These *E. coli* inclusions are composed of protein aggregates. In addition, inclusions can contain phosphate reserves, sulfur reserves, or photosynthetic pigments.

Key Points

- The cytosol contains the liquid portion of the cytoplasm and is not contained within a membrane -bound component.
- Macromolecules within the cytoplasm include DNA, ribosomes and proteins.
- Cytoplasmic inclusions within the cytoplasm are characterized by a granular appearance and vary based on cell type.

Key Terms

- **hopanoids**: a group of pentacyclic compounds that exhibit various functions in prokaryotes

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6.1B: Sources of Essential Nutrients

Learning Objectives

- Describe the types of nutrients that are used by microorganisms for growth and metabolism

Nutrients are materials that are acquired from the environment and are used for growth and metabolism. Microorganisms (or microbes) vary significantly in terms of the source, chemical form, and amount of essential elements they need. Some examples of these essential nutrients are carbon, oxygen, hydrogen, phosphorus, and sulfur. There are two categories of essential nutrients: macro-nutrients (which are needed in large amounts) and micro-nutrients (which are needed in trace or small amounts). Macro-nutrients usually help maintain the cell structure and metabolism. Micro-nutrients help enzyme function and maintain protein structure.

Organic and Inorganic Nutrients

Organic nutrients contain some combination of carbon and hydrogen atoms. Inorganic nutrients are elements or simply molecules that are made of elements other than carbon and hydrogen.

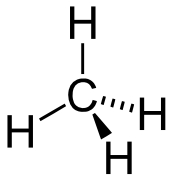

Figure: ***Methane, a simple organic molecule****: Methane is one of the simplest organic molecules.*

Essential Nutrients

The sources of common essential nutrients are carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur. Organisms usually absorb carbon when it is in its organic form. Carbon in its organic form is usually a product of living things. Another essential nutrient, nitrogen, is part of the structure of protein, DNA, RNA, and ATP. Nitrogen is important for heterotroph survival, but it must first be degraded into basic building blocks, such as amino acids, in order to be used. Oxygen is an important component of both organic and inorganic compounds. It is essential to the metabolism of many organisms. Hydrogen has many important jobs including maintaining the pH of solutions and providing free energy in reactions of respiration. Phosphate is an important player in making nucleic acids and cellular energy transfers. Without sufficient phosphate, an organism will cease to grow. Lastly, sulfur is found in rocks and sediments and is found widely in mineral form.

Key Points

- Nutrients are materials that are acquired from the environment and are used for growth and metabolism. Microorganisms (or microbes) vary significantly in the source, chemical form, and amount they will need of these essential elements.
- Macro-nutrients are needed in large amounts and micro-nutrients are needed in trace or small amounts.
- Organic nutrients contain some combination of carbon and hydrogen atoms. Inorganic nutrients are elements or simply molecules that are made of elements other than carbon and hydrogen.

Key Terms

- **organic**: relating to the compounds of carbon, and relating to natural products
- **inorganic**: relating to a compound that does not contain carbon.
- **metabolism**: the complete set of chemical reactions that occur in living cells.

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6.1C: Limitation of Microbial Growth by Nutrient Supply

Learning Objectives

- Describe the role of nutrients in microbial growth and their culture in the lab

Nutrients are necessary for microbial growth and play a vital role in the proper cultivation of microorganisms in the laboratory and for proper growth in their natural environments. The types of nutrients that are required include those that supply energy, carbon and additional necessary materials. The nutrients used to propagate growth are organism -specific, based on their cellular and metabolic processes..



Figure: ***Anthrax Culture****: An image of an anthrax culture grown on a petri dish. For microoganisms to be cultured in the laboratory or undergo successful growth in their natural environment, the proper nutrients are absolutely necessary.*

The common nutrients which are found to be required in all living things include carbon, nitrogen, sulfur, phosphorus, potassium, magnesium, calcium, oxygen, iron and additional trace elements. Essential nutrients are nutrients absolutely required by an organism. Two categories of essential nutrients are macro- and micro-nutrients. Macronutrients are necessary in large amounts; micronutrients tend to be needed in smaller amounts and are often trace elements.

Nutrients as Limiting Factors

In regard to required nutrients for proper growth, there are often limiting factors involved. The limiting factor or limiting nutrient affects and controls growth. The availability of specific nutrients dictates organismal growth by controlling and limiting activation of cellular and metabolic pathways necessary for progress. When all nutrients and parameters are ideal and constant during the growth phase, this is regarded as a steady state: all requirements are present and microorganisms thrive. In circumstances where there are less than ideal parameters, such as a lack of specific requirements, the growth process is affected.

In industrial microbiology this concept is critical, as microbial growth and production is dictated by proper cellular growth and metabolism. The production of necessary components if often controlled by the presence and concentration of a limiting nutrient. Hence, it is critical to identify the required nutrients and ensure these are supplied in the culturing of microorganisms.

Key Points

- The common nutrients which are found to be required in all living things include carbon, nitrogen, sulfur, phosphorus, potassium, magnesium, calcium, oxygen, iron and additional trace elements.
- Both and macro- and micro-nutrients are critical in proper organismal growth as they play important roles in cellular and metabolic processes.
- The limiting nutrient is essential for growth and based on its concentration and presence or absence can control growth.

Key Terms

- **micronutrient**: an element or nutrient required in small quantities.
- **macronutrients**: any element or nutrient required in large amounts.

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SECTION OVERVIEW

6.2: Cell Differentiation and Starvation

Topic hierarchy

6.2A: Activation of Starvation by Survival Genes

6.2B: Oligotrophs

6.2C: Starvation-Induced Fruiting Bodies

6.2D: Bacterial Differentiation

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6.2A: Activation of Starvation by Survival Genes

Stringent response is a stress response that occurs in bacteria and plant chloroplasts in reaction to stress conditions.

Learning Objectives

- Discuss how starvation activates survival genes

Key Points

- The stringent response is signaled by the alarmone (p)ppGpp.
- In Escherichia coli (p)ppGpp, production is mediated by the ribosomal protein L11 and the ribosome-associated protein RelA with the A-site bound deacylated tRNA being the ultimate inducer.
- In other bacteria, stringent response is mediated by a variety of RelA/SpoT Homologue (RSH) proteins, some of which activate synthetically, hydrolytically, or both (Rel).

Key Terms

- **stringent response**: a stress response in bacteria in reaction to amino-acid starvation, fatty acid limitation, and other stress conditions.

Stringent Response, also called stringent control, is a stress response that occurs in bacteria and plant chloroplasts in reaction to amino-acid starvation, fatty acid limitation, iron limitation, heat shock, and other stress conditions. The stringent response is signaled by the alarmone (p)ppGpp and modulating transcription of up to 1/3 of all genes in the cell. This in turn causes the cell to divert resources away from growth and division and toward amino acid synthesis in order to promote survival until nutrient conditions improve.

In *Escherichia coli*, (p)ppGpp production is mediated by the ribosomal protein L11 and the ribosome-associated protein RelA with the A-site bound deacylated tRNA being the ultimate inducer. RelA converts GTP and ATP into pppGpp by adding the pyrophosphate from ATP onto the 3′ carbon of the ribose in GTP, releasing AMP. pppGpp is converted to ppGpp by the *gpp* gene product, releasing Pi. ppGpp is converted to GDP by the *spoT* gene product, releasing pyrophosphate (PPi). GDP is converted to GTP by the *ndk* gene product. Nucleoside triphosphate (NTP) provides the Pi, and is converted to Nucleoside diphosphate (NDP).

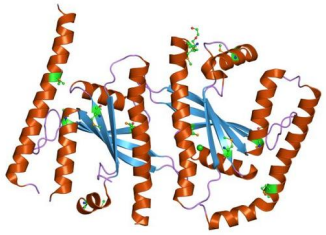

Figure: **RelA/ SpoT protein homologue**: In bacteria stringent response is mediated by a variety of RelA/SpoT Homologue (RSH) proteins.

In other bacteria, stringent response is mediated by a variety of RelA/SpoT Homologue (RSH) proteins. Some of these proteins activate synthetically, hydrolytically, or both (Rel). The disabling of the stringent response by distruption of relA and spoT in *Pseudomonas aeruginosa*, produced in infectious cells and biofilms characterized by nutrient limitation, causes greater susceptibility to antibiotics.

During the stringent response, (p)ppGpp accumulation affects the resource-consuming cell processes replication, transcription, and translation. (p)ppGpp is thought to bind RNA polymerase and alter the transcriptional profile, decreasing the synthesis of translational machinery (such as rRNA and tRNA), and increasing the transcription of biosynthetic genes. Additionally, the initiation of new rounds of replication is inhibited and the cell cycle arrests until nutrient conditions improve. Translational GTPases involved in protein biosynthesis are also affected by ppGpp, with Initiation Factor 2 (IF2) being the main target.

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6.2B: Oligotrophs

Learning Objectives

- Examine oligotrophs and their adaptation to nutrient poor environments

An oligotroph is an organism that thrives in an environment that offers very low levels of nutrients. They may be contrasted with copiotrophs, which prefer nutritionally rich environments. Oligotrophs are characterized by slow growth, low rates of metabolism, and generally low population density. Oligotrophic environments include deep oceanic sediments, caves, glacial and polar ice, deep subsurface soil, aquifers, ocean waters, and leached soils. An ecosystem or environment is said to be oligotrophic if it offers little to sustain life. The term is commonly utilized to describe environments of water, ice, air, rock or soil with very low nutrient levels. Oligotrophic environments are of special interest for alternative energy sources and survival strategies upon which life could rely. An example of oligotrophic bacterium are *Caulobacter crescentus*.



Figure: ***Extremophiles****: These hot springs are an example of harsh environments that some extremophiles can grow in.*

Caulobacter crescentus is a Gram-negative, oligotrophic bacterium widely distributed in fresh water lakes and streams. The control circuitry that directs and paces Caulobacter cell cycle progression involves the entire cell operating as an integrated system. The control circuitry monitors the environment and the internal state of the cell, including the cell topology, as it orchestrates activation of cell cycle subsystems and Caulobacter crescentus asymmetric cell division. The proteins of the Caulobacter cell cycle control system and its internal organization are co-conserved across many alphaproteobacteria species, but there are great differences in the regulatory apparatus' functionality and peripheral connectivity to other cellular subsystems from species to species. The Caulobacter cell cycle control system has been exquisitely optimized by evolutionary selection as a total system for robust operation in the face of internal stochastic noise and environmental uncertainty.

The bacterial cell's control system has a hierarchical organization. The signaling and the control subsystem interfaces with the environment by means of sensory modules largely located on the cell surface. The genetic network logic responds to signals received from the environment and from internal cell status sensors to adapt the cell to current conditions.

Key Points

- Oligotrophic environments are of special interest for alternative energy sources and survival strategies upon which life could rely.

Key Terms

- **oligotroph**: An organism capable of living in an environment that offers very low levels of nutrients.

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6.2C: Starvation-Induced Fruiting Bodies

Starvation-induced fruiting bodies can aggregate up to 500 micrometres long and contain approximately 100,000 bacterial cells.

Learning Objectives

- Explain starvation induced fruit bodies

Key Points

- In fruiting bodies, the bacteria perform separate tasks; this type of cooperation is a simple type of multicellular organisation.
- *Myxococcus xanthus* colonies exist as a self-organized, predatory single- species biofilm called a swarm.
- The fruiting process is thought to benefit *myxobacteria* by ensuring that cell growth is resumed with a group (swarm) of *myxobacteria*, rather than as isolated cells.

Key Terms

- **quorum sensing**: A proposed method of communication between bacterial cells by the release and sensing of small diffusible signal molecules.
- **stigmergy**: A mechanism of spontaneous, indirect coordination between agents or actions, where the trace left in the environment by an action stimulates the performance of a subsequent action.
- **saprotrophic**: Extra-cellular digestion involved in the processing of dead or decayed organic matter

Starvation-Induced Fruiting Bodies

When starved of amino acids, *myxobacteria*, or slime bacteria, detect surrounding cells in a process known as *quorum sensing* . Migrating towards each other, they aggregate to form fruiting bodies up to 500 micrometers long containing approximately 100,000 bacterial cells. In these fruiting bodies, the bacteria perform separate tasks; this type of cooperation is a simple type of multicellular organisation. About one in 10 cells migrate to the top of these fruiting bodies and differentiate into a specialized dormant state called *myxospore*, which is more resistant to drying and other adverse environmental conditions than ordinary cells.

The *myxobacteria* are a group of bacteria that predominantly live in the soil and feed on insoluble organic substances. The *myxobacteria* have very large genomes, relative to other bacteria e.g., 9–10 million nucleotides. *Sorangium cellulosum* has the largest known (as of 2008) bacterial genome, at 13.0 million nucleotides.

Myxobacteria are included among the delta group of *proteobacteria*, a large taxon of Gram-negative forms. They can move actively by gliding and typically travel in swarms (also known as wolf packs), containing many cells kept together by intercellular molecular signals. Individuals benefit from aggregation as it allows accumulation of extracellular enzymes which are used to digest food that increases feeding efficiency.

Myxobacteria produce a number of biomedically and industrially-useful chemicals, such as antibiotics, and export those chemicals outside of the cell. When nutrients are scarce, myxobacterial cells aggregate into fruiting bodies, a process long-thought to be mediated by chemotaxis but now considered to be a function of a form of contact-mediated signaling. These fruiting bodies can take different shapes and colors, depending on the species.



Figure: **Bacteria use cell signaling to communicate**: A swarm of M. xanthus is a distributed system: a population of millions of identical entities that communicate among themselves in a non-centralized fashion, thus behaving as a single entity.

Within the fruiting bodies, cells begin as rod-shaped vegetative cells and develop into rounded myxospores with thick cell walls. These myxospores, analogous to spores in other organisms, are more likely to survive until nutrients are more plentiful. The fruiting process is thought to benefit *myxobacteria* by ensuring that cell growth is resumed with a group (swarm) of *myxobacteria*, rather than as isolated cells. At a molecular level, initiation of fruiting body development is regulated by Pxr sRNA.

Myxococcus xanthus colonies exist as a self-organized, predatory, saprotrophic, single-species biofilm called a swarm. *Myxococcus xanthus*, which can be found almost ubiquitously in soil, are thin rod-shaped, gram-negative cells that exhibit self-organizing behavior as a response to environmental cues. The swarm modifies its environment through *stigmergy*. This behavior facilitates predatory feeding, as the concentration of extracellular digestive enzymes secreted by the bacteria increases.

M. xanthus is a model organism for studying development, the behavior in which starving bacteria self-organize to form fruiting bodies: dome shaped structures of approximately 100,000 cells. These swarms differentiate into metabolically quiescent and environmentally resistant myxospores over the course of several days. During this process of self-organizing, dense ridges of cells move in traveling waves (ripples) that grow and shrink over several hours.

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6.2D: Bacterial Differentiation

Several bacteria alter their morphology in response to the types and concentrations of external compounds.

Learning Objectives

- Explain bacterial differentiation to eukaryotic-like sturctures

Key Points

- Bacterial morphology changes help to optimize interactions with cells and the surfaces to which they attach.
- Oxidative stress, nutrient limitation, DNA damage and antibiotics exposure are some of stress conditions to which bacteria respond, altering their DNA replication and cell division.
- The most frequent shape alteration may be filamentation triggered by a limitation in the availability of one or more nutrients.

Key Terms

- **cytoskeleton**: A cellular structure like a skeleton, contained within the cytoplasm.
- **septum**: a partition that separates the cells of a (septated) fungus
- **segrosomes**: multiprotein complexes that partition chromosomes/plasmids in bacteria.
- **cell division**: a process by which a cell divides into two cells.

Bacterial morphological plasticity refers to evolutionary changes in the shape and size of bacterial cells. As bacteria evolve, morphological changes occur to maintain the consistency of the cell. However, this consistency could be affected in some circumstances (such as environmental stress) and changes in bacterial shape and size. In bacteria, the transformation into filamentous organisms have been recently demonstrated. These are survival strategies that affect the normal physiology of the bacteria in response to factors such as innate immune response, predator sensing, quorum sensing and antimicrobial signs.

Normally, bacteria have different shapes and sizes which include coccus, rod and helical/spiral (among others less common). This forms the basis for their classification. For instance, rod shapes may allow bacteria to attach more readily in environments with shear stress (e.g., in flowing water). Cocci may have access to small pores, creating more attachment sites per cell and hiding themselves from external shear forces. Spiral bacteria combine some of the characteristics of cocci (small footprints) and of filaments (more surface area on which shear forces can act) and the ability to form an unbroken set of cells to build biofilms. Several bacteria alter their morphology in response to the types and concentrations of external compounds. Bacterial morphology changes help to optimize interactions with cells and the surfaces to which they attach. This mechanism has been described in bacteria such as Escherichia coli and Helicobacter pylori.



Figure: **Electron micrograph of H. pylori possessing multiple flagella (negative staining)**: Several bacteria alter their morphology in response to the types and concentrations of external compounds.This has been described in bacteria such as E. coli and H. pylori.

Oxidative stress, nutrient limitation, DNA damage and antibiotics exposure are some stress conditions to which bacteria respond, altering their DNA replication and cell division. Filamentous bacteria have been considered to be over-stressed, sick and dying members of the population. However, the filamentous members of some communities have vital roles in the population's continued existence, since the filamentous phenotype can confer protection against lethal environments.Filamentous *E. coli* can be up to 70 µm in length and has been identified as playing an important role in pathogenesis in human cystitis. There are different mechanisms identified in some bacteria that are attributable to the development of filamentous forms.

Nutritional stress can change bacterial morphology. The most frequent shape alteration may be filamentation triggered by a limitation in the availability of one or more nutrients. Since the filament can increase a cell's uptake–proficiency surface without changing its surface-to-volume ratio appreciably, this may be enough reason for cells to be filament. Moreover, the filamentation benefits bacterial cells attaching to a surface because it increases specific surface area in direct contact with the solid medium. In addition, the filamentation may allow bacterial cells to access nutrients by enhancing the possibility that the filament will be exposed to a nutrient-rich zone and pass compounds to the rest of the cell's biomass. For example, *Actinomyces israelii* grows as filamentous rods or branched in the absence of phosphate, cysteine, or glutathione. However, it returns to a regular rod-like morphology when adding back these nutrients.

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SECTION OVERVIEW

6.3: Culturing Bacteria

Topic hierarchy

6.3A: Culture Media

6.3B: Complex and Synthetic Media

6.3C: Selective and Differential Media

6.3D: Aseptic Technique, Dilution, Streaking, and Spread Plates

6.3E: Special Culture Techniques

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6.3A: Culture Media

Learning Objectives

- Classify culture media

Culture medium or growth medium is a liquid or gel designed to support the growth of microorganisms. There are different types of media suitable for growing different types of cells. Here, we will discuss microbiological cultures used for growing microbes, such as bacteria or yeast.

NUTRIENT BROTHS AND AGAR PLATES

These are the most common growth media, although specialized media are sometimes required for microorganism and cell culture growth. Some organisms, termed fastidious organisms, need specialized environments due to complex nutritional requirements. Viruses, for example, are obligate intracellular parasites and require a growth medium containing living cells. Many human microbial pathogens also require the use of human cells or cell lysates to grow on a media.

The most common growth media nutrient broths (liquid nutrient medium) or LB medium (Lysogeny Broth) are liquid. These are often mixed with agar and poured into Petri dishes to solidify. These agar plates provide a solid medium on which microbes may be cultured. They remain solid, as very few bacteria are able to decompose agar. Many microbes can also be grown in liquid cultures comprised of liquid nutrient media without agar.



Figure: **Microbial pathogen growing on blood-agar plate**: Red blood cells are used to make an agar plate. Different pathogens that can use red blood cells to grow are shown on these plates. On the left is staphylococcus and the right streptococcus.

DEFINED VS UNDEFINED MEDIA

This is an important distinction between growth media types. A *defined* medium will have known quantities of all ingredients. For microorganisms, it provides trace elements and vitamins required by the microbe and especially a defined carbon and nitrogen source. Glucose or glycerol are often used as carbon sources, and ammonium salts or nitrates as inorganic nitrogen sources. An *undefined* medium has some complex ingredients, such as yeast extract, which consists of a mixture of many, many chemical species in unknown proportions. Undefined media are sometimes chosen based on price and sometimes by necessity – some microorganisms have never been cultured on defined media.

There are many different types of media that can be used to grow specific microbes, and even promote certain cellular processes; such as wort, the medium which is the growth media for the yeast that makes beer. Without wort in certain conditions, fermentation cannot occur and the beer will not contain alcohol or be carbonated (bubbly).

COMMON BROADLY-DEFINED CULTURE MEDIA

Nutrient media – A source of amino acids and nitrogen (e.g., beef, yeast extract). This is an undefined medium because the amino acid source contains a variety of compounds with the exact composition being unknown. These media contain all the elements that most bacteria need for growth and are non-selective, so they are used for the general cultivation and maintenance of bacteria kept in laboratory-culture collections.

Minimal media – Media that contains the minimum nutrients possible for colony growth, generally without the presence of amino acids, and are often used by microbiologists and geneticists to grow “wild type” microorganisms. These media can also be used to

select for or against the growth of specific microbes. Usually a fair amount of information must be known about the microbe to determine its minimal media requirements.

Selective media – Used for the growth of only selected microorganisms. For example, if a microorganism is resistant to a certain antibiotic, such as ampicillin or tetracycline, then that antibiotic can be added to the medium in order to prevent other cells, which do not possess the resistance, from growing.

Differential media – Also known as indicator media, are used to distinguish one microorganism type from another growing on the same media. This type of media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators (such as neutral red, phenol red, eosin y, or methylene blue) added to the medium to visibly indicate the defining characteristics of a microorganism. This type of media is used for the detection and identification of microorganisms.

These few examples of general media types provide some indication only; there are a myriad of different types of media that can be used to grow and control microbes.

Key Points

- Culture media contains the nutrients needed to sustain a microbe.
- Culture media can vary in many ingredients allowing the media to select for or against microbes.
- Glucose or glycerol are often used as carbon sources, and ammonium salts or nitrates as inorganic nitrogen sources in culture media.

Key Terms

- **culture**: The process of growing a bacterial or other biological entity in an artificial medium.
- **lysogeny broth**: Lysogeny broth (LB) is a nutritionally-rich medium; primarily used for the growth of bacteria.

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6.3B: Complex and Synthetic Media

In defined media all the chemical compounds are known, while undefined media has partially unknown chemical constituents.

Learning Objectives

- Differentiate complex and synthetic medias

Key Points

- Defined media is made from constituents that are completely understood.
- Undefined media has some part of which is not entirely defined.
- The presence of extracts from animals or other microbes makes a media undefined as the entire chemical composition of extracts are not completely known.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **serum**: The clear yellowish fluid obtained upon separating whole blood into its solid and liquid components after it has been allowed to clot. Also called blood serum.

There are many types of culture media, which is food that microbes can live on. Two major sub types of media are complex and synthetic medias, known as undefined and defined media.



Figure: **Undefined Media**: Luria Broth as shown here is made with yeast extract, as yeast extract is not completely chemically defined Luria Broth is therefore an undefined media. By Lilly_M [GFDL (http://www.gnu.org/copyleft/fdl.html), CC-BY-SA, via Wikimedia Commons

An undefined medium has some complex ingredients, such as yeast extract or casein hydrolysate, which consist of a mixture of many, many chemical species in unknown proportions. Undefined media are sometimes chosen based on price and sometimes by necessity – some microorganisms have never been cultured on defined media.A defined medium (also known as chemically defined medium or synthetic medium) is a medium in which all the chemicals used are known, no yeast, animal, or plant tissue is present. A chemically defined medium is a growth medium suitable for the culture of microbes or animal cells (including human) of which all of the chemical components are known. The term chemically defined medium was defined by Jayme and Smith as a 'Basal formulation which may also be protein-free and is comprised solely of biochemically-defined low molecular weight constituents.

A chemically defined medium is entirely free of animal-derived components (including microbial derived components such as yeast extract) and represents the purest and most consistent cell culture environment. By definition chemically defined media cannot contain either fetal bovine serum, bovine serum albumin, or human serum albumin as these products are derived from bovine or human sources and contain complex mixes of albumins and lipids. The term ‘chemically defined media’ is often misused in the literature to refer to serum albumin-containing media. Animal serum or albumin is routinely added to culture media as a source of nutrients and other ill-defined factors, despite technical disadvantages to its inclusion and its high cost. Technical disadvantages to using serum include the undefined nature of serum, batch-to-batch variability in composition, and the risk of contamination. There are increasing concerns about animal suffering inflicted during serum collection that add an ethical imperative to move away from the use of serum wherever possible. Chemically defined media differ from serum-free media in that bovine serum albumin or human serum albumin with either a chemically defined recombinant version (which lacks the albumin associated lipids) or synthetic chemical such as the polymer polyvinyl alcohol which can reproduce some of the functions of serums.

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6.3C: Selective and Differential Media

Learning Objectives

- Compare selective and differential media

There are many types of media used in the studies of microbes. Two types of media with similar implying names but very different functions, referred to as selective and differential media, are defined as follows.

Selective media are used for the growth of only selected microorganisms. For example, if a microorganism is resistant to a certain antibiotic, such as ampicillin or tetracycline, then that antibiotic can be added to the medium in order to prevent other cells, which do not possess the resistance, from growing. Media lacking an amino acid such as proline in conjunction with *E. coli* unable to synthesize it were commonly used by geneticists before the emergence of genomics to map bacterial chromosomes. Selective growth media are also used in cell culture to ensure the survival or proliferation of cells with certain properties, such as antibiotic resistance or the ability to synthesize a certain metabolite. Normally, the presence of a specific gene or an allele of a gene confers upon the cell the ability to grow in the selective medium. In such cases, the gene is termed a marker. Selective growth media for eukaryotic cells commonly contain neomycin to select cells that have been successfully transfected with a plasmid carrying the neomycin resistance gene as a marker. Gancyclovir is an exception to the rule as it is used to specifically kill cells that carry its respective marker, the Herpes simplex virus thymidine kinase (HSV TK). Some examples of selective media include:

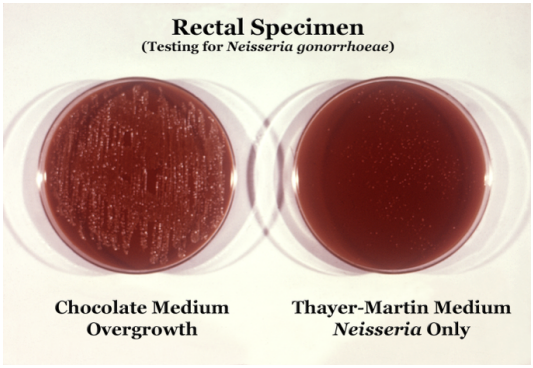

Figure: **Non-selective versus selective media.**: The non-selective media on the right allows of the growth of several different bactarial species and is overgrown with bacteria (whitish lines). While the plate on the right selectively only allows the bacteria Neisseria gonorrhoeae, to grow (white dots).

- Eosin methylene blue (EMB) that contains methylene blue – toxic to Gram-positive bacteria, allowing only the growth of Gram negative bacteria.
- YM (yeast and mold) which has a low pH, deterring bacterial growth.
- MacConkey agar for Gram-negative bacteria.
- Hektoen enteric agar (HE) which is selective for Gram-negative bacteria.
- Mannitol salt agar (MSA) which is selective for Gram-positive bacteria and differential for mannitol.
- Terrific Broth (TB) is used with glycerol in cultivating recombinant strains of Escherichia coli.
- Xylose lysine desoxyscholate (XLD), which is selective for Gram-negative bacteria buffered charcoal yeast extract agar, which is selective for certain gram-negative bacteria, especially Legionella pneumophila.

Differential media or indicator media distinguish one microorganism type from another growing on the same media. This type of media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators (such as neutral red, phenol red, eosin y, or methylene blue) added to the medium to visibly indicate the defining characteristics of a microorganism. This type of media is used for the detection of microorganisms and by molecular biologists to detect recombinant strains of bacteria. Examples of differential media include:

- Blood agar (used in strep tests), which contains bovine heart blood that becomes transparent in the presence of hemolytic.
- Streptococcuseosin methylene blue (EMB), which is differential for lactose and sucrose fermentation.
- MacConkey (MCK), which is differential for lactose fermentationmannitol salt agar (MSA), which is differential for mannitol fermentation.
- X-gal plates, which are differential for lac operon mutants.

Key Points

- Selective media generally selects for the growth of a desired organism, stopping the growth of or altogether killing non-desired organisms.
- Differential media takes advantage of biochemical properties of target organisms, often leading to a visible change when growth of target organisms are present.
- Differential media, unlike selective media, does not kill organisms. It indicates if a target organism is present.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **gene**: A unit of heredity; a segment of DNA or RNA that is transmitted from one generation to the next. It carries genetic information such as the sequence of amino acids for a protein.
- **allele**: One of a number of alternative forms of the same gene occupying a given position on a chromosome.

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6.3D: Aseptic Technique, Dilution, Streaking, and Spread Plates

Microbiologists rely on aseptic technique, dilution, colony streaking and spread plates for day-to-day experiments.

Learning Objectives

- Recall aseptic technique, dilution series, streaking and spreading plates

Key Points

- Aseptic technique is basically the mindset of keeping things free of contamination, as the world we live in has so many microbes that can interfere with experiments.
- Colony streaking leads to to the isolation of individual colonies, which are a group of microbes that came from one single progenitor mircrobe.
- Spread plates allow for the even spreading of bacteria onto a petri dish; allowing for the isolation of individual colonies, for counting or further experiments.

Key Terms

- **colony**: A bacterial colony is defined as a visible cluster of bacteria growing on the surface of or within a solid medium, presumably cultured from a single cell.
- **bunsen burner**: A small laboratory gas burner whose air supply may be controlled with an adjustable hole.

Microbiologists have many tools, but four relatively simple techniques are used by microbiologists daily, these are outlined here.

Aseptic technique or sterile technique is used to avoid contamination of sterile media and equipment during cell culture. Sterile technique should always be employed when working with live cell cultures and reagents/media that will be used for such cultures. This technique involves using flame to kill contaminating organisms, and a general mode of operation that minimizes exposure of sterile media and equipment to contaminants.

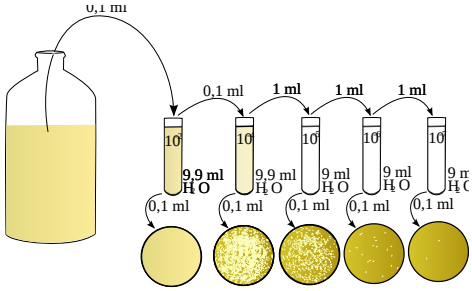

Figure: **Serial Dilution**: Example of Serial dilution of bacteria in five steps. The diluted bacteria were then spread plated. By Leberechtc (Own work) [GFDL (http://www.gnu.org/copyleft/fdl.html) and CC-BY-3.0 (http://creativecommons.org/licenses/by/3.0)], via Wikimedia Commons

When working with cultures of living organisms, it is extremely important to maintain the environments in which cells are cultured and manipulated as free of other organisms as possible. This requires that exposure of containers of sterilized culture media to outside air should be minimized, and that flame is used to “re-sterilize” container lids and rims. This means passing rims and lids through the flame produced by a Bunsen burner in order to kill microorganisms coming in contact with those surfaces.

Sterile technique, in general, is a learned state-of-being, or mantra, where every utilization of any sterile material comes with the caveat of taking every precaution to ensure it remains as free of contaminants as possible for as long as possible. Heat is an excellent means of killing microorganisms, and the Bunsen burner is the sterile technician’s best friend.

A serial dilution is the step-wise dilution of a substance in solution. Usually the dilution factor at each step is constant, resulting in a geometric progression of the concentration in a logarithmic fashion. A ten-fold serial dilution could be 1 M, 0.1 M, 0.01 M, 0.001 M… Serial dilutions are used to accurately create highly-diluted solutions as well. A culture of microbes can be diluted in the same fashion. For a ten-fold dilution on a 1 mL scale, vials are filled with 900 microliters of water or media, and 100 microliters of the stock microbial solution are serially transferred, with thorough mixing after every dilution step. The dilution of microbes is very important to get to microbes diluted enough to count on a spread plate (described later).

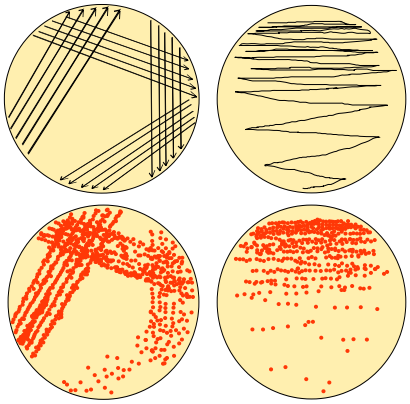

Figure: **Streak plate**: Four streak plates. Successful streaks lead to individual colonies of microbes.

In microbiology, streaking is a technique used to isolate a pure strain from a single species of microorganism, often bacteria. Samples can then be taken from the resulting colonies and a microbiological culture can be grown on a new plate so that the organism can be identified, studied, or tested.The streaking is done using a sterile tool, such as a cotton swab or commonly an inoculation loop. This is dipped in an inoculum such as a broth or patient specimen containing many species of bacteria.The sample is spread across one quadrant of a petri dish containing a growth medium, usually an agar plate which has been sterilized in an autoclave. Choice of which growth medium is used depends on which microorganism is being cultured, or selected for. Growth media are usually forms of agar, a gelatinous substance derived from seaweed.

Spread plates are simply microbes spread on a media plate. Microbes are in a solution, and can be diluted. They are then transferred to a petri dish with media specific for the growth of the microbe of interest. The solution is then spread uniformly through a number of possible means, the most popular is the use of sterile glass beads that are shook on top of the media, spreading the microbe-containing liquid evenly on the plate. Also common is the use of a bent-glass rod, often referred to as a hockey stick, due to its similar shape. The glass rod is sterilized and used to spread the microbe-containing liquid uniformly on the plate.

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6.3E: Special Culture Techniques

Learning Objectives

- Evaluate special culture techniques

Microbiologists would prefer to use well-defined media to grow a microbe, making the microbe easier to control. However, microbes are incredibly varied in what they use as a food source, the environments they live in, and the danger levels they may have for humans and other organisms they may compete with. Therefore they need special nutrient and growth environments. To grow these difficult microbes, microbiologists often turn to undefined media which is chosen based on price and more-so in this case by necessity as some microorganisms have never been cultured on defined media. Some special culture conditions are relatively simple as demonstrated by microaerophile.

A microaerophile is a microorganism that requires oxygen to survive, but requires environments containing lower levels of oxygen than are present in the atmosphere (~20% concentration). Many microphiles are also capnophiles, as they require an elevated concentration of carbon dioxide. In the laboratory they can be easily cultivated in a candle jar. A candle jar is a container into which a lit candle is introduced before sealing the container's airtight lid. The candle's flame burns until extinguished by oxygen deprivation, which creates a carbon dioxide-rich, oxygen-poor atmosphere in the jar. Many labs also have access directly to carbon dioxide and can add the desired carbon dioxide levels directly to incubators where they want to grow microaerophiles.

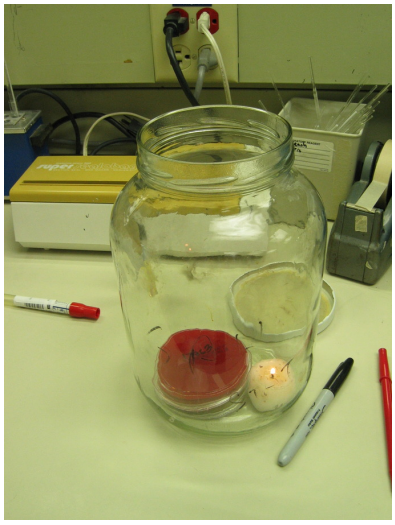

Figure: ***Candle jar****: A candle is lit in a jar with a culture plate. The lid is put on, as the burns it increases the carbon dioxide levels in the jar.*

Animals can often be used to culture microbes. For example, armadillos are often used in the study of leprosy. They are particularly susceptible due to their unusually low body temperature, which is hospitable to the leprosy bacterium, Mycobacterium leprae. The leprosy bacterium is difficult to culture and armadillos have a body temperature of 34°C, similar to human skin. Likewise, humans can acquire a leprosy infection from armadillos by handling them or consuming armadillo meat. Additionally, Syphillis which is caused by the bacteria *Treponema pallidum* is difficult to grow with defined media, so rabbits are used to culture *Treponema pallidum*. *Treponema pallidum* belongs to the Spirochaetesphylum of bacteria.

To date Spirochaetes are very difficult if not impossible to rear in a controlled laboratory environment. This also includes other human pathogens like the bacterium that causes Lyme disease. Using animals to culture human-pathogens has problems. First, the use of animals is always difficult for technical and ethical reasons. Also, a microbe growing on animal other than a human may behave very differently from how that same microbe will behave on a human. Some human pathogens are grown directly on cells cultured from humans. Exemplified by the bacteria *Chlamydia trachomatis*, the bacteria responsible for the sexually transmitted infection (STI) in humans known as Chlamydia. As *Chlamydia trachomatis* only grows in humans. The human cell culture known as McCoy cell culture is used to culture this bacteria.

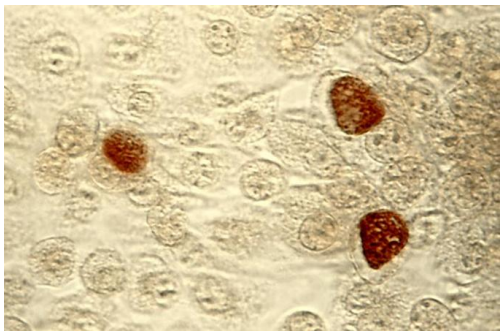

Figure: ***Chlamydias bacteria group****: Light microscope view of cells infected with chlamydiae as shown by the brown inclusion bodies.*

A large concern of microbiology is trying to find ways in which humans can avoid or get rid of microbrial infections. As typified by some of the above examples, some microbes have to be grown in the lab, and some of them can infect humans. To deal with this, microbiologists use a classification of biosafety levels. A biosafety level is the level of the biocontainment precautions required to isolate dangerous biological agents in an enclosed facility. The levels of containment range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). In the United States, the Centers for Disease Control and Prevention (CDC) have specified these levels.

- **Biosafety Level 1**: This level is suitable for work involving well-characterized agents not known to consistently cause disease in healthy adult humans, with minimal potential hazard to laboratory personnel and the environment.
- **Biosafety Level 2**: This level is similar to Biosafety Level 1 and is suitable for work involving agents of moderate potential hazard to personnel and the environment. It includes various bacteria and viruses that cause only mild disease to humans or are difficult to contract via aerosol in a lab setting such as chlamydia.
- **Biosafety Level 3**: This level is applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents that may cause serious or potentially lethal disease after inhalation. It includes various bacteria, parasites, and viruses that can cause severe to fatal disease in humans, but for which treatments exist (eg. yellow fever).
- **Biosafety Level 4**: This level is reserved for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections, agents that cause severe to fatal disease in humans for which vaccines or other treatments are not available, such as Bolivian and Argentine hemorrhagic fevers, Marburg virus, and the Ebola virus. Very few laboratories are biosafety level 4.



Figure: **Positive pressure suit**: A scientist puts on a positive pressure suit, something needed to work with the most dangerous human pathogens in a biosafety level 4 laboratory.

Key Points

- Microbes, often those that we know little about, have to be cultured with undefined media or growth conditions.
- The use of animals to culture animals is sometimes necessary as no simple media can be used, this presents technical and ethical issues.
- As human pathogens are often studied by microbiologists, special safety conditions know as biosafety levels are used to keep researches free of infection from the pathogens they study.

Key Terms

- **yellow fever**: An acute febrile illness of tropical regions, caused by a flavivirus and spread by mosquitoes, characterized by jaundice, black vomit, and the absence of urination.
- **Lyme disease**: Infection by a bacterium of the genus Borrelia which is transmitted by ticks. Symptoms include a rash followed by fever, joint pain, and headaches.

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SECTION OVERVIEW

6.4: Microbial Culture Methods

Topic hierarchy

6.4A: Enrichment and Isolation

6.4B: Pure Culture

6.4C: Preserving Bacterial Cultures

6.4D: The FISH Technique

6.4E: Coupling Specific Genes to Specific Organisms Using PCR

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6.4A: Enrichment and Isolation

Learning Objectives

- List the growth phases of microrganisms and the different types of growth media available to culture them

The most common growth media for microorganisms are nutrient broths and agar plates; specialized media are required for some microorganisms. Some, termed *fastidious organisms*, require specialized environments due to complex nutritional requirements. Viruses, for example, are obligate intracellular parasites and require a growth medium containing living cells.

Growth media: defined vs. undefined

An important distinction between growth media types is that of defined versus undefined media.

A defined medium will have known quantities of all ingredients. For microorganisms, this consists of providing trace elements and vitamins required by the microbe, and especially, a defined source of both carbon and nitrogen. Glucose or glycerol is often used as carbon sources, and ammonium salts or nitrates as inorganic nitrogen sources.

An undefined medium has some complex ingredients, such as yeast extract or casein hydrolysate, which consist of a mixture of many, many chemical species in unknown proportions. Undefined media are sometimes chosen based on price and sometimes by necessity – some microorganisms have never been cultured on defined media.

Types of media

Enriched media contain the nutrients required to support the growth of a wide variety of organisms, including some of the more fastidious ones. They are commonly used to harvest as many different types of microbes as are present in the specimen. Blood agar is an enriched medium in which nutritionally-rich whole blood supplements the basic nutrients. Chocolate agar is enriched with heat-treated blood (40-45°C), which turns brown and gives the medium the color for which it is named.

Selective media are used for the growth of only selected microorganisms. For example, if a microorganism is resistant to a certain antibiotic, such as *ampicillin*or *tetracycline*, then that antibiotic can be added to the medium in order to prevent other cells, which do not possess the resistance, from growing. Media lacking an amino acid, such as proline in conjunction with E. coli unable to synthesize it, were commonly used by geneticists before the emergence of genomics to map bacterial chromosomes.



Figure: ***TSI Agar slant tubes****: The agar triple-sugar iron is one of the culture media used for the differentiation of most enterobacteria.*

Differential/indicator media distinguish one microorganism type from another growing on the same media. This type of media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators (such as neutral red, phenol red, eosin y, or methylene blue) added to the medium to visibly indicate the defining characteristics of a microorganism. This type of media is used for the detection of microorganisms and by molecular biologists to detect recombinant strains of bacteria. The agar triple-sugar iron (TSI) is one of the culture media used for the differentiation of most enterobacteria.

Growth in closed culture systems, such as a batch culture in LB broth, where no additional nutrients are added and waste products are not removed, the bacterial growth will follow a predicted growth curve and can be modeled.

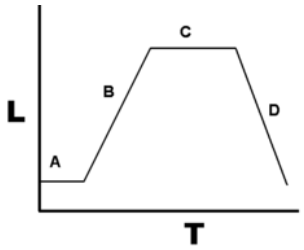

Figure: **Bacterial growth curve**: Bacterial growth in batch culture can be modeled with four different phases: lag phase (A), exponential or log phase (B), stationary phase (C), and death phase (D).

Growth phases

During lag phase, bacteria adapt themselves to growth conditions. It is the period where the individual bacteria are maturing and not yet able to divide. During the lag phase of the bacterial growth cycle, synthesis of RNA, enzymes and other molecules occurs.

Exponential phase (sometimes called the log or logarithmic phase) is a period characterized by cell doubling. The number of new bacteria appearing per unit time is proportional to the present population.Under controlled conditions, cyanobacteria can double their population four times a day. Exponential growth cannot continue indefinitely, however, because the medium is soon depleted of nutrients and enriched with wastes.

The stationary phase is due to a growth-limiting factor; this is mostly depletion of a nutrient, and/or the formation of inhibitory products such as organic acids.

At death phase, bacteria run out of nutrients and die.

Culture

Batch culture is the most common laboratory-growth method in which bacterial growth is studied, but it is only one of many. The bacterial culture is incubated in a closed vessel with a single batch of medium.

In some experimental regimes, some of the bacterial culture is periodically removed and added to fresh sterile medium. In the extreme case, this leads to the continual renewal of the nutrients. This is a *chemostat*, also known as an open or continuous culture: a steady state defined by the rates of nutrient supply and bacterial growth. In comparison to batch culture, bacteria are maintained in exponential growth phase, and the growth rate of the bacteria is known. Related devices include *turbidostats* and *auxostats*. Bacterial growth can be suppressed with bacteriostats, without necessarily killing the bacteria.

In a synecological culture, a true-to-nature situation in which more than one bacterial species is present, the growth of microbes is more dynamic and continual.

Key Points

- The most common growth media for microorganisms are nutrient broths and agar plates.
- Open cultures allow for a replenishment of nutrients and a reduction of waste buildup in the media.
- Selective media are used for the growth of only selected microorganisms.
- Differential media or indicator media distinguish one microorganism type from another growing on the same media.

Key Terms

- **closed culture**: A closed culture has no additional nutrients added to the system, and waste products are not removed. Cultures in a closed system will follow a predicted growth curve.
- **Enriched media**: Contains nutrients required to support the growth of a wide variety of organisms.
- **open culture**: A continuous culture where periodically some of the bacterial culture is removed and added to fresh sterile medium.

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6.4B: Pure Culture

Learning Objectives

- Describe how pure microbial cultures can be grown in agar-based growth medium

Microbial cultures are foundational and basic diagnostic methods used extensively as a research tool in molecular biology. It is often essential to isolate a pure culture of microorganisms. A pure (or axenic) culture is a population of cells or multicellular organisms growing in the absence of other species or types. A pure culture may originate from a single cell or single organism, in which case the cells are genetic clones of one another. For the purpose of gelling the microbial culture, the medium of agarose gel (agar) is used. Agar is a gelatinous substance derived from seaweed. A cheap substitute for agar is guar gum, which can be used for the isolation and maintenance of thermophiles.

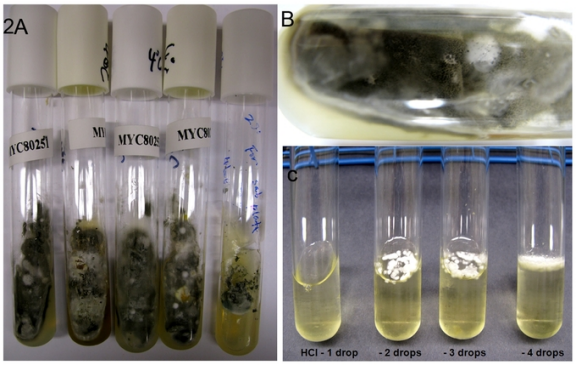

Figure: ***Selective Media***: *Geomyces destructans in culture from bat tissues. (A) Original culture tubes of Sabouraud agar supplemented with nine antibiotics and incubated at 4°C for six- or eight-weeks; notice the profuse growth of G. destructans strains. (B) Some fungal contamination on individual isolates was visible as depicted in the close-up of a culture tube. (C) Enrichment and recovery of pure fungal colonies by treating a culture contaminated with bacteria with hydrochloric acid.*

Microbiological cultures can be grown in petri dishes of differing sizes that have a thin layer of agar-based growth medium. Once the growth medium in the petri dish is inoculated with the desired bacteria, the plates are incubated at the best temperature for the growing of the selected bacteria (for example, usually at 37 degrees Celsius for cultures from humans or animals or lower for environmental cultures). Another method of bacterial culture is liquid culture, in which the desired bacteria are suspended in liquid broth, a nutrient medium. These are ideal for preparation of an antimicrobial assay. The experimenter would inoculate liquid broth with bacteria and let it grow overnight (they may use a shaker for uniform growth). Then they would take aliquots of the sample to test for the antimicrobial activity of a specific drug or protein (antimicrobial peptides). As an alternative, the microbiologist may decide to use static liquid cultures. These cultures are not shaken and they provide the microbes with an oxygen gradient.

Key Points

- A pure culture may originate from a single cell or single organism, in which case the cells are genetic clones of one another.
- Microbial cultures are foundational and basic diagnostic methods used extensively as a research tool in molecular biology.
- The most common form of microbial cultures are liquid or solid (agar).

Key Terms

- **agar**: A gelatinous material obtained from the marine algae, used as a bacterial culture medium, in electrophoresis and as a food additive.

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6.4C: Preserving Bacterial Cultures

Learning Objectives

- Describe how bacterial cultures can be stored for a long time at -80 °C in glycerol

Three species of bacteria, *Carnobacterium pleistocenium*, *Chryseobacterium greenlandensis*, and *Herminiimonas glaciei*, have reportedly been revived after surviving for thousands of years frozen in ice. As a practical matter, as a researcher, you will want to preserve your selected bacteria so you can go back to it if something goes wrong. Whenever you successfully transform a bacterial culture with a plasmid or whenever you obtain a new bacterial strain, you will want to make a long term stock of that bacteria. Bacteria can be stored for months and years if they are stored at -80 °C and in a high percentage of glycerol.



Figure: ***Bacteria in liquid media****: An erlenmeyer containing a bacterial culture. Bacteria that have been preserved in glycerol stocks can be grown overnight in liquid media to promote propagation.*

In order to ensure a pure culture is being preserved, pick a single colony of the bacteria off a plate, grow it overnight in the appropriate liquid media, and with shaking. Take the overnight culture and and mix an aliquot with 40% glycerol in sterile water and place in a cryogenic vial. It is important to label the vial with all the relevant information (e.g. strain, vector, date, researcher, etc.). Freeze the glycerol stock and store at -80 °C. At this point you should also record the strain information and record the location.

While it is possible to make a long term stock from cells in the stationary phase, ideally your culture should be in logarithmic growth phase. Certain antibiotics in the medium should be removed first as they are supposedly toxic over time, e.g. Tetracycline. To do this, spin the culture down and resuspend it in the same volume of straight LB medium.

Key Points

- Preserve your selected bacteria so you always have something to go back to if something goes wrong.
- While it is possible to make a long term stock from cells in stationary phase, ideally your culture should be in logarithmic growth phase.
- Ensure a pure culture is being preserved by picking a single colony of the bacteria off a plate for cryopreservation.

Key Terms

- **cryogenic**: of, relating to, or performed at low temperatures
- **logarithmic growth phase**: exponential phase (sometimes called the log phase or the logarithmic phase) is a period characterized by cell doubling.

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6.4D: The FISH Technique

Learning Objectives

- Describe how fluorescent in situ hybridization (FISH) is used in clinical and biomedical studies to detect and localize the presence or absence of specific DNA sequences and to identify pathogens

FISH (fluorescence in situ hybridization) is a cytogenetic technique developed by biomedical researchers in the early 1980s. It is used to detect and localize the presence or absence of specific DNA sequences on chromosomes. FISH uses fluorescent probes bind to those targets that show a high degree of sequence complementarity. FISH can be used to detect RNA or DNA sequences of interest. FISH is often used for finding specific features in DNA for use in genetic counseling, medicine, and species identification. FISH can also be used to detect and localize specific RNA targets, including mRNAs, in cells. In this context, it can help define the spatial-temporal patterns of gene expression within cells and tissues.

Central to FISH are the use of probes. The probe must be large enough to hybridize specifically with its target but not so large as to impede the hybridization process. They are anti-sense to the target mRNA or DNA of interest, thus they hybridize to targets. The probe can be tagged directly with fluorophores, or with targets for flourescently labelled antibodies or other substrates. Different types of tags can be used, therefore different targets can be detected in the same sample simultaneously (multi-colour FISH). Tagging can be done in various ways, such as nick translation, or PCR using tagged nucleotides. Probes can vary in length from 20 to 30 nucleotides to much longer sequences.

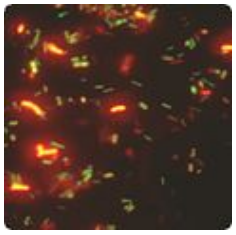

Figure: **Dual label FISH image**: Here is an example of FISH being used to differentiate Bifidobacteria (red) and other bacteria (green)

FISH is often used in clinical studies. If a patient is infected with a suspected pathogen, bacteria from the patient's tissues or fluids, are typically grown on agar to determine the identity of the pathogen. Many bacteria, however, even well-known species, do not grow well under laboratory conditions. FISH can be used to directly detect the presence of the suspect on small samples of the patient's tissue. FISH can also be used to compare the genomes of two biological species, to deduce evolutionary relationships. A similar hybridization technique is called a zoo blot. Bacterial FISH probes are often primers for the 16s rRNA region. FISH is widely used in the field of microbial ecology, to identify microorganisms. Biofilms, for example, are composed of complex (often) multi-species bacterial organizations. Preparing DNA probes for one species and performing FISH with this probe allows one to visualize the distribution of this specific species within the biofilm. Preparing probes (in two different colors) for two species allows to visualize/study co-localization of these two species in the biofilm, and can be useful in determining the fine architecture of the biofilm.

Key Points

- FISH can be used in a clinical setting to identify pathogens or DNA / RNA targets of interest.
- FISH is used to detect and localize the presence or absence of specific DNA or RNA sequences in tissue or cells.
- FISH can also be used to compare the genomes of two biological species, such as in ecological studies, where a bacteria may not be culturable, it can be identified using FISH.

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6.4E: Coupling Specific Genes to Specific Organisms Using PCR

Learning Objectives

- Describe how polymerase chain reaction (PCR) allows for the amplification and mutation of DNA and enables researchers to study very small samples

Polymerase chain reaction (PCR) is a useful technique for scientists, because it allows for the amplification and mutation of DNA. Through PCR, small quantities of DNA can be replicated by orders of magnitude, not only essentially preserving the sample if successful, but allowing for study on a much larger scale.. Without PCR, the studies we perform would be limited by the amount of DNA we were able to isolate from samples. Through PCR, the original DNA is essentially limitless, allowing scientists to induce various mutations in different genes for further study.

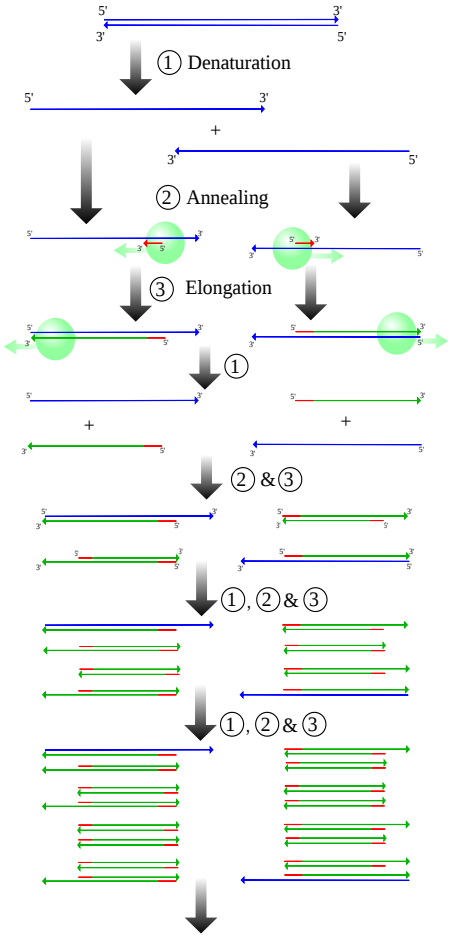

Figure: ***Polymerase chain reaction****: a schematic of the polymerase chain reaction*

Through site-directed mutagenesis or customized primers, individual mutations in DNA can be made. By changing the amino acids transcribed from DNA through individual mutations, the importance of those amino acids with respect to gene function can be analyzed. However, this process can be difficult, particularly when genes act in concert (with varying expression with respect to gene activity). The length of time it takes to run a successful PCR and perform other techniques before additional studies can be done (protein expression, isolation, and purification, for example), makes biochemical research time-consuming and difficult. However, PCR, coupled with other biochemical techniques, allows us to analyze the very core of organisms and the processes by which they function. Common PCR protocols in labs today include knockout genotyping, fluorescence genotyping and mutant genotyping. Researchers can use PCR as a method of searching for genes by using primers that flank the target sequence of the gene along with all other necessary components for PCR. If the gene is present, the primers will bind and amplify the DNA, giving

a band of amplified DNA on the agarose gel that will be run. If the gene is not present, the primers will not anneal and no amplification will occur.

The ability to identify specific genes to specific organisms has increased the use of PCR and has allowed it to be more specific and eliminate the possibility of cross contaminants. The identification of specific genes to specific organisms has important medical diagnostic value.

PCR is a reliable method to detect the presence of unwanted genetic materials, such as infections and bacteria in the clinical setting. It can even allow identification of an infectious agent without culturing. For example, in diagnosis of diseases like AIDS, PCR can be used to detect the small percentage of cells that are infected with HIV by utilizing primers that are specific for genes specialized to the HIV virus. PCR can reveal the presence of HIV in people who have not mounted an immune response to this pathogen, which may otherwise be missed with an antibody assay). Additionally, PCR is used for identifying bacterial species, such as *Mycobacterium tuberculosis* in tissue specimens. With the use of PCR, as few as 10 bacilli per million human cells can be readily detected. The bacilli are identified by using *Mycobacterium tuberculosis* specific genes.

Key Points

- PCR allows for identification of an infectious agent without the need for culturing.
- Researchers can use PCR as a method of searching for specific genes and/or mutations.
- PCR, coupled with other biochemical techniques, allows us to analyze the very core of organisms and the processes by which they function.

Key Terms

- **polymerase chain reaction**: A technique in molecular biology for creating multiple copies of DNA from a sample; used in genetic fingerprinting etc.

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SECTION OVERVIEW

6.5: Bacterial Population Growth

Topic hierarchy

6.5A: Chemical Assays, Radioisotopic Methods, and Microelectrodes

6.5B: Stable Isotopes

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6.5A: Chemical Assays, Radioisotopic Methods, and Microelectrodes

There are numerous tests and assays available that are utilized to aid in bacterial identification in a variety of settings.

Learning Objectives

- Contrast the different tests that can be used in studies of microbes

Key Points

- Chemical assays used for bacterial identification utilize various components of the microorganisms including structural, cellular and metabolic indicators.
- Radioisotopic methods include the use of radioisotopes to help identify specific metabolic pathways utilized by bacteria by tracking uptake and breakdown of specific nutrients labeled with radioactivity.
- Micro-electrodes are commonly being used in bacterial identification, specifically for pathogenic bacteria, as a means to identify biological components in a variety of environments by combining with bio-sensors.

Key Terms

- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.

Within the field of microbiology, there are specific tests or assays utilized to quantitatively and qualitatively measure microorganism components. These assays are often utilized to aid in bacterial identification. Three major types used for this purpose include chemical assays, radio isotopic methods and the use of micro electrodes. The following is an overview of these methodologies.

Chemical Assays

Chemical assays are utilized to identify and determine chemical components within a microorganism. Many of these assays test for specific cellular components and may have overlap with chemical analysis, which focuses on exact chemical composition.

Gram Staining

Examples of chemical assays include the classic test for Gram-positive or Gram-negative bacteria via Gram staining. Gram staining is utilized to differentiate bacteria into either of these Gram groups. The Gram staining technique is based on both chemical and physical properties of bacterial cell walls and tests for the presence of peptidoglycan.

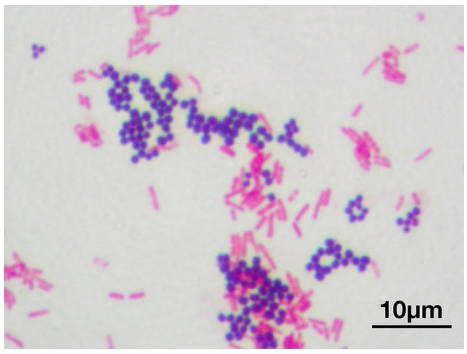

Figure: **Gram Staining**: An example of a chemical assay used for bacterial identification.

Oxidative-Fermentation Glucose Test

The O-F test is utilized to determine the way in which a bacteria is capable of metabolizing carbohydrates such as glucose. The two major mechanisms from which bacteria can obtain energy include oxidation of glucose and lactose fermentation. This specific assay identifies which method bacteria use by cultivating bacteria in various conditions.

Hydrolysis Tests

The process of hydrolysis is characterized by the ability to chemically split a molecule by the addition of water. There are numerous tests utilized in bacterial identification which involve testing for hydrolysis of specific substances. These tests include

hydrolysis of starch, lipids, casein and gelatin. The basis of these tests is to identify and determine if a microbe has the proper enzymes and molecules to breakdown and use these specific molecules as sources of energy for cellular growth.

Radioisotopic Methods

Radioisotopes are specific types of isotopes that emit radioactivity. Isotopes of an element vary in the number of neutrons within their nuclei. In the field of microbiology, radioisotopes have been used

Micro-electrodes

Electrodes are characterized by a system of electrical conductors that are used to make contact with a non-metallic portion of a circuit. In regards to microbiology and bacterial identification, micro-electrodes are commonly being utilized to identify pathogenic bacteria in numerous settings. The micro-electrodes have the capability to function as bio-sensors and detect specific biological components of microbes.

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6.5B: Stable Isotopes

Learning Objectives

- Demonstrate how isotopes are used in bacterial identification

The term isotope refers to the number of neutrons a certain element contains. Elements of the same name (for example, oxygen) must always have the same number of protons, but the number of neutrons can change. Adding or subtracting neutrons from an atom does not change the elemental properties, but it can alter some of its features (like making it more radioactive).

Stable Isotopes

While the number of neutrons in a particular atom can change, there is a certain threshold where the atom is given more neutrons that its nuclear force can hold. At this point, the neutrons start to be released. The release is also known as decay. During this time, the atom is deemed “unstable. ” The atom will continue to lose neutrons until it become stable again. A stable isotope is a chemical isotope that is not radioactive. There are some cases where atoms have no stable isotopes so they continue to lose neutrons, and later protons and electrons, until they become another element entirely. Research has shown that there are 80 elements with one or more stable isotopes. Of these, 26 have only one stable isotope which is also known as being monoisotopic. The element with the most stable isotopes is tin which as 10 stable isotopes.

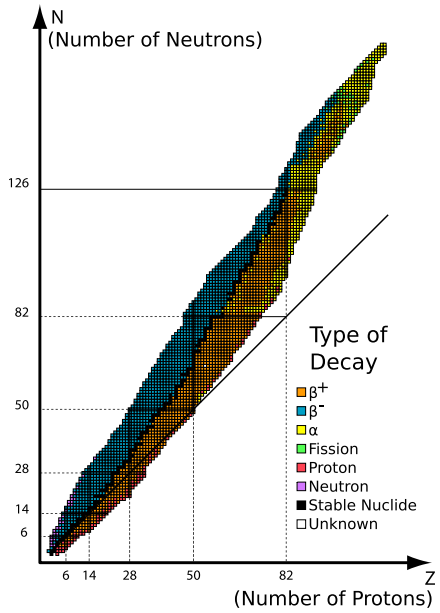

Figure: **Table of Isotopes**: This is a table that represents atom decay yielding various isotopes.

Key Points

- The term isotope refers to the number of neutrons a certain element contains.
- Elements of the same name must always have the same number of protons, but the number of neutrons can change.
- Adding or subtracting neutrons from an atom does not change the elemental properties, but it can alter some of its features (like making it more radioactive).
- While the number of neutrons in a particular atom can change, there is a certain threshold where the atom is given more neutrons that its nuclear force can hold. At this point, the atom is deemed unstable.
- The atom will continue to lose neutrons, or decay, until it become stable again. A stable isotope is a chemical isotope that is not radioactive.

Key Terms

- **isotope**: Any of two or more forms of an element where the atoms have the same number of protons, but a different number of neutrons within their nuclei. As a consequence, atoms for the same isotope will have the same atomic number but a different mass number (atomic weight).

- **atom**: The smallest possible amount of matter which still retains its identity as a chemical element, now known to consist of a nucleus surrounded by electrons.
- **Radioactive**: A particle that has spontaneous emission of ionizing radiation as a consequence of a nuclear reaction, or directly from the breakdown of an unstable nucleus.

Extensions

Knowledge about stable isotopes is important in a variety of fields. Scientists have used information on these topics in botanical and plant biological investigations as well as ecological and biological studies. Additionally, some scientists have used oxygen isotope ratios to reconstruct historical atmospheric temperatures. This work is especially important due to our current concern with climate change/global warming.

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SECTION OVERVIEW

6.6: Microbial Growth

Topic hierarchy

6.6A: Binary Fission

6.6B: Fts Proteins and Cell Division

6.6C: MreB and Determinants of Cell Morphology

6.6D: Peptidoglycan Synthesis and Cell Division

6.6E: Generation Time

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6.6A: Binary Fission

Learning Objectives

- Describe the process of binary fission in prokaryotes

Prokaryotes, such as bacteria, propagate by binary fission. For unicellular organisms, cell division is the only method used to produce new individuals. In both prokaryotic and eukaryotic cells, the outcome of cell reproduction is a pair of daughter cells that are genetically identical to the parent cell. In unicellular organisms, daughter cells are individuals.

Due to the relative simplicity of the prokaryotes, the cell division process, or binary fission, is a less complicated and much more rapid process than cell division in eukaryotes. The single, circular DNA chromosome of bacteria is not enclosed in a nucleus, but instead occupies a specific location, the nucleoid, within the cell. Although the DNA of the nucleoid is associated with proteins that aid in packaging the molecule into a compact size, there are no histone proteins and thus, no nucleosomes in prokaryotes. The packing proteins of bacteria are, however, related to the cohesin and condensin proteins involved in the chromosome compaction of eukaryotes.

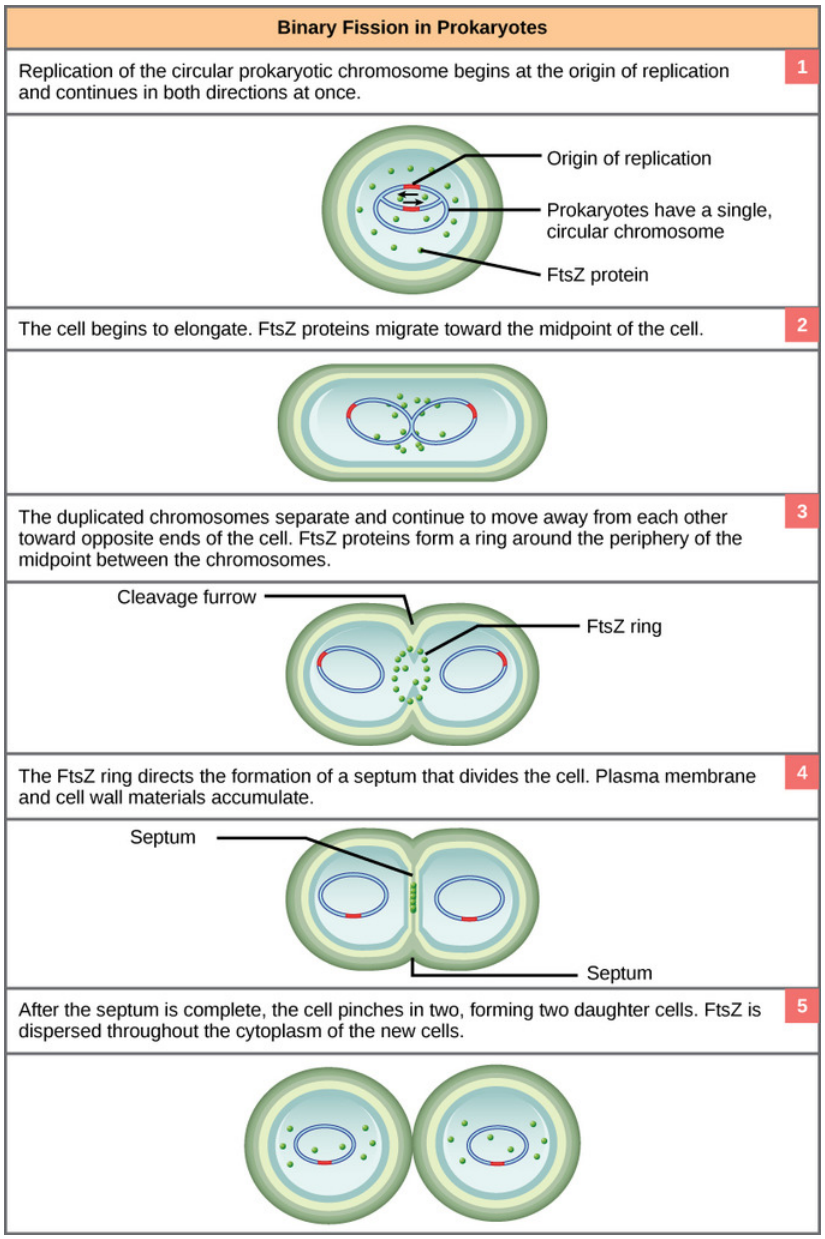

Figure: **Binary Fission**: These images show the steps of binary fission in prokaryotes.

https://bio.libretexts.org/@go/page/9177

The bacterial chromosome is attached to the plasma membrane at about the midpoint of the cell. The starting point of replication, the origin, is close to the binding site of the chromosome at the plasma membrane. Replication of the DNA is bidirectional, moving away from the origin on both strands of the loop simultaneously. As the new double strands are formed, each origin point moves away from the cell wall attachment toward the opposite ends of the cell. As the cell elongates, the growing membrane aids in the transport of the chromosomes. After the chromosomes have cleared the midpoint of the elongated cell, cytoplasmic separation begins. The formation of a ring composed of repeating units of a protein, FtsZ, directs the partition between the nucleoids. Formation of the FtsZ ring triggers the accumulation of other proteins that work together to recruit new membrane and cell wall materials to the site. A septum is formed between the nucleoids, extending gradually from the periphery toward the center of the cell. When the new cell walls are in place, the daughter cells separate.

Mitotic Spindle Apparatus

The precise timing and formation of the mitotic spindle is critical to the success of eukaryotic cell division. Prokaryotic cells, on the other hand, do not undergo karyokinesis and, therefore, have no need for a mitotic spindle. However, the FtsZ protein that plays such a vital role in prokaryotic cytokinesis is structurally and functionally very similar to tubulin, the building block of the microtubules that make up the mitotic spindle fibers that are necessary for eukaryotes. FtsZ proteins can form filaments, rings, and other three-dimensional structures that resemble the way tubulin forms microtubules, centrioles, and various cytoskeletal components. In addition, both FtsZ and tubulin employ the same energy source, GTP (guanosine triphosphate), to rapidly assemble and disassemble complex structures.

FtsZ and tubulin are homologous structures derived from common evolutionary origins. In this example, FtsZ is the ancestor protein to tubulin (a modern protein). While both proteins are found in extant organisms, tubulin function has evolved and diversified tremendously since evolving from its FtsZ prokaryotic origin. A survey of mitotic assembly components found in present-day unicellular eukaryotes reveals crucial intermediary steps to the complex membrane-enclosed genomes of multicellular eukaryotes.

Key Points

- In bacterial replication, the DNA is attached to the plasma membrane at about the midpoint of the cell.
- The origin, or starting point of bacterial replication, is close to the binding site of the DNA to the plasma membrane.
- Replication of the bacterial DNA is bidirectional, which means it moves away from the origin on both strands simultaneously.
- The formation of the FtsZ ring, a ring composed of repeating units of protein, triggers the accumulation of other proteins that work together to acquire and bring new membrane and cell wall materials to the site.
- When new cell walls are in place, due to the formation of a septum, the daughter cells separate to form individual cells.

Key Terms

- **mitotic spindle**: the apparatus that orchestrates the movement of DNA during mitosis
- **karyokinesis**: (mitosis) the first portion of mitotic phase where division of the cell nucleus takes place
- **binary fission**: the process whereby a cell divides asexually to produce two daughter cells

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6.6B: Fts Proteins and Cell Division

FtsZ is a protein encoded by the ftsZ gene that assembles into a ring at the future site of the septum of bacterial cell division.

LEARNING OBJECTIVES

Evaluate the role of Fts proteins in cell division

Key Takeaways

Key Points

- FtsZ has been named after “Filamenting temperature-sensitive mutant Z”.
- During cell division, FtsZ is the first protein to move to the division site, and is essential for recruiting other proteins that produce a new cell wall between the dividing cells.
- FtsZ’s role in cell division is analogous to that of actin in eukaryotic cell division, but unlike the actin-myosin ring in eukaryotes, FtsZ has no known motor protein associated with it.

Key Terms

- **segrosomes**: multiprotein complexes that partition chromosomes/plasmids in bacteria.
- **cell division**: a process by which a cell divides into two cells.
- **septum**: a partition that separates the cells of a (septated) fungus
- **cytoskeleton**: A cellular structure like a skeleton, contained within the cytoplasm.

FtsZ is a protein encoded by the ftsZ gene that assembles into a ring at the future site of the septum of bacterial cell division. This is a prokaryotic homologue to the eukaryotic protein tubulin. FtsZ has been named after “Filamenting temperature-sensitive mutant Z”. The hypothesis was that cell division mutants of E. coli would grow as filaments due to the inability of the daughter cells to separate from one another.

FtsZ was the first protein of the prokaryotic cytoskeleton to be identified. During cell division, FtsZ is the first protein to move to the division site, and is essential for recruiting other proteins that produce a new cell wall between the dividing cells. FtsZ’s role in cell division is analogous to that of actin in eukaryotic cell division, but unlike the actin-myosin ring in eukaryotes, FtsZ has no known motor protein associated with it. The origin of the cytokinetic force thus remains unclear, but it is believed that the localized synthesis of new cell wall produces at least part of this force. It is interesting to note that L-form bacteria that lack a cell wall do not require FtsZ for division, which implies that bacteria may have retained components of an ancestral mode of cell division.

Much is known about the dynamic polymerization activities of tubulin and microtubules, but little is known about these activities in FtsZ. While it is known that single-stranded tubulin protofilaments form into 13 stranded microtubules, the multistranded structure of the FtsZ-containing Z-ring is not known. It is only speculated that the structure consists of overlapping protofilaments. Recently, proteins similar to tubulin and FtsZ have been discovered in large plasmids found in Bacillus species. They are believed to function as components of segrosomes, which are multiprotein complexes that partition chromosomes/plasmids in bacteria. The plasmid homologs of tubulin/FtsZ seem to have conserved the ability to polymerize into filaments.

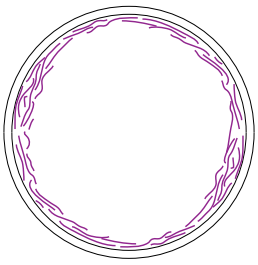

Figure: **FtsZ Filaments**: The Z-ring forms from smaller subunits of FtsZ filaments. These filaments may pull on each other and tighten to divide the cell.

FtsZ has the ability to bind to GTP, and also exhibits a GTPase domain that allows it to hydrolyze GTP to GDP and a phosphate group. In vivo, FtsZ forms filaments with a repeating arrangement of subunits, all arranged head-to-tail. These filaments form a ring around the longitudinal midpoint, or septum, of the cell. This ring is called the Z-ring. The GTP hydrolyzing activity of the

protein is not essential to the formation of filaments or division. Mutants lacking the GTPase domain form twisted and disordered septa. These cells with irregular septa can still divide, although abnormally. It is unclear as to whether FtsZ actually provides the physical force that results in division or serves as a marker for other proteins to execute division.

The Z-ring forms from smaller subunits of FtsZ filaments. These filaments may pull on each other and tighten to divide the cell. If FtsZ does provide force that divides the cell, it may do so through the relative movement of subunits. In this model, FtsZ scission force comes from the relative lateral movement of subunits. Lines of FtsZ would line up together parallel and pull on each other creating a “cord” of many strings that tightens itself. In other models, FtsZ does not provide the contractile force but provides the cell a spatial scaffold for other proteins to execute the division of the cell. This is akin to the creating of a temporary structure by construction workers to access hard-to-reach places of a building. The temporary structure allows unfettered access and ensures that the workers can reach all places. If the temporary structure is not correctly built, the workers will not be able to reach certain places, and the building will be deficient.

This “scaffold theory” is supported by information that shows that the formation of the ring and localization to the membrane requires the concerted action of a number of accessory proteins. ZipA or the actin homologue FtsA permit initial FtsZ localization to the membrane. Following localization to the membrane, division proteins of the Fts family are recruited for ring assembly. Many of these proteins, such as FtsW, FtsK, and FtsQ are involved in stabilization of the Z ring and may also be active participants in the scission event. The formation of the Z-ring closely coincides with cellular processes associated with replication.

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6.6C: MreB and Determinants of Cell Morphology

MreB is a protein found in bacteria homologous to actin.

LEARNING OBJECTIVES

Explain the role of MreB in cell morphology determination

Key Takeaways

Key Points

- MreB proteins polymerize to form filaments that are similar to actin microfilaments.
- MreB controls the width of rod-shaped bacteria, such as Escherichia coli.
- Bacteria that are naturally spherical do not have the gene encoding MreB.

Key Terms

- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.
- **cell wall**: A thick, fairly rigid layer formed around individual cells of bacteria, Archaea, fungi, plants, and algae, the cell wall is external to the cell membrane and helps the cell maintain its shape and avoid damage.
- **cytoskeleton**: A cellular structure like a skeleton, contained within the cytoplasm.



Figure: **Atomic structure of MreB, a prokaryotic structural protein**: Procaryotic MreB in cartoon representation. The fold of the protein is similar to its eukaryotic counterpart

MreB is a protein found in bacteria that has been identified as a homologue of actin, as indicated by similarities in tertiary structure and conservation of active site peptide sequence. The conservation of protein structure suggests the common ancestry of the cytoskeletal elements formed by actin and MreB, found in prokaryotes. Indeed, recent studies have found that MreB proteins polymerize to form filaments that are similar to actin microfilaments.MreB controls the width of rod-shaped bacteria, such as Escherichia coli. A mutant E. coli that creates defective MreB proteins will be spherical instead of rod-like. Also, bacteria that are naturally spherical do not have the gene encoding MreB. Prokaryotes carrying the mreB gene can also be helical in shape. MreB has long been thought to form a helical filament underneath the cytoplasmic membrane. However, this model has been brought into question by three recent publications showing that filaments cannot be seen by electron cryotomography and that GFP-MreB can be seen as patches moving around the cell circumference. It has also been shown to interact with several proteins that are proven to be involved in length growth (for instance PBP2). Therefore, MreB probably directs the synthesis and insertion of new peptidoglycan building units into the existing peptidoglycan layer to allow length growth of the bacteria.

MreB is a cytoskeleton element that assembles into filamentous structures within the bacterial cytoplasm. MreB and its homologs have been shown to interact and co-localize with cytoplasmic protein(MurB-G), membrane-imbedded proteins (MreD, MraY and RodA), as well as other molecules with large periplasmic domain in organism. Recent research shows that peptidoglycan precursors are inserted into cell wall following helical pattern which is dependent on MreB, and it’s reported that MreB also promote the GT activity of PBPs. This ability of MreB is because of RodZ, an inner membrane protein containing an 80-residue, N-terminal cytoplasmic region, and a 200-amino acid periplasmic C-terminal tail. RodZ co-localizes with MreB helices in a

manner that is strictly dependent on its cytoplasmic region. MreB- RodZ complexes act as a major stabilizing factor in bacterial cell wall and ensure the insertion of new peptidoglycan in a spiral like fashion into the cell wall.

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6.6D: Peptidoglycan Synthesis and Cell Division

Learning Objectives

- Examine Peptidoglycan synthesis during cell division

Peptidoglycan, also known as murein, is a polymer consisting of sugars and amino acids that forms a mesh-like layer outside the plasma membrane of bacteria (but not Archaea; []), forming the cell wall. The sugar component consists of alternating residues of β-(1,4) linked N-acetylglucosamine and N-acetylmuramic acid. Attached to the N-acetylmuramic acid is a peptide chain of three to five amino acids. The peptide chain can be cross-linked to the peptide chain of another strand forming the 3D mesh-like layer. Some Archaea have a similar layer of pseudopeptidoglycan or pseudomurein, where the sugar residues are β-(1,3) linked N-acetylglucosamine and N-acetyltalosaminuronic acid. That is why the cell wall of Archaea is insensitive to lysozymes, which are present in human sweat and tears as part of innate immunity.

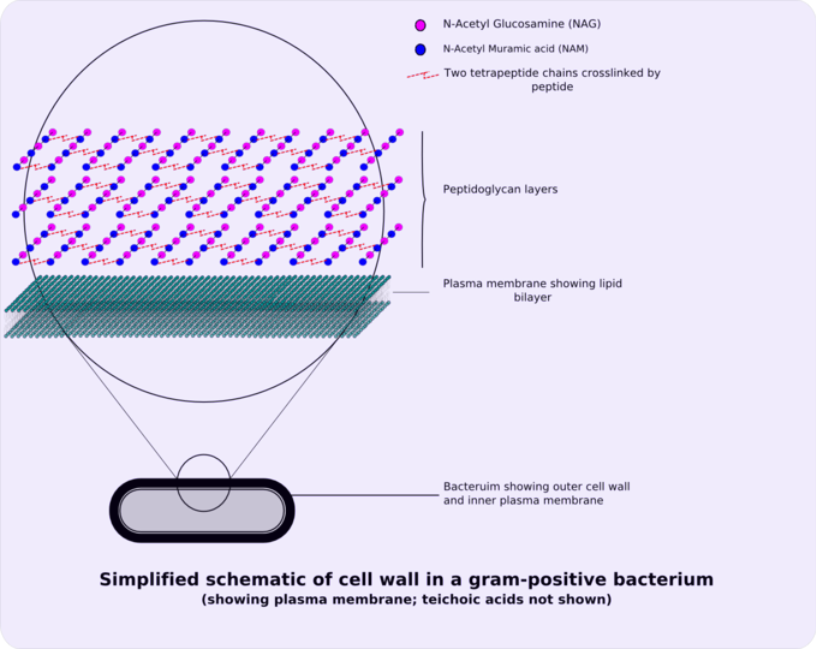

Figure: ***Simplified sc hematic of a cell wall in a Gram-positive bacteria****: Cross-linking between amino acids in different linear amino sugar chains occurs with the help of the enzyme transpeptidase and results in a 3-dimensional structure that is strong and rigid.*

Peptidoglycan serves a structural role in the bacterial cell wall giving it strength, as well as counteracting the osmotic pressure of the cytoplasm. A common misconception is that peptidoglycan gives the cell its shape. However, it is actually the MreB protein that facilitates cell shape. Peptidoglycan is also involved in binary fission during bacterial cell reproduction.

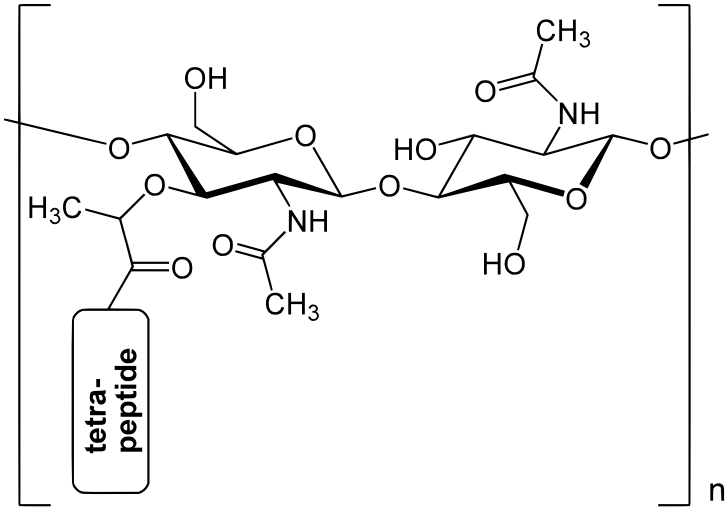

Figure: ***Peptidoglycan structure****: The peptidoglycan layer in the bacterial cell wall is a crystal lattice structure formed from linear chains of two alternating amino sugars, namely N-acetylglucosamine (GlcNAc or NAG) and N-acetylmuramic acid (MurNAc or NAM).*

The peptidoglycan layer is substantially thicker in Gram-positive bacteria (20 to 80 nanometers) than in Gram-negative bacteria (7 to 8 nanometers), with the attachment of the S-layer. Peptidoglycan forms around 90% of the dry weight of Gram-positive bacteria but only 10% of Gram-negative strains. Thus, presence of high levels of peptidoglycan is the primary determinant of the characterization of bacteria as gram-positive. In Gram-positive strains, it is important in attachment roles and stereotyping purposes. For both Gram-positive and Gram-negative bacteria, particles of approximately 2 nm can pass through the peptidoglycan. Gram-positive and Gram-negative bacteria are sensitive to different types of antiobiotics.

Key Points

- The sugar component of peptidoglycan consists of alternating residues of β-(1,4) linked N-acetylglucosamine and N-acetylmuramic acid.
- Peptidoglycan serves a structural role in the bacterial cell wall, giving structural strength but not shape, and counteracting the osmotic pressure of the cytoplasm.
- Peptidoglycan is also involved in binary fission during bacterial cell reproduction.

Key Terms

- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.
- **MreB**: MreB is a protein found in bacteria that has been identified as a homologue of actin, as indicated by similarities in tertiary structure and conservation of active site peptide sequence.

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6.6E: Generation Time

Learning Objectives

- Examine microbial generation times

Bacterial growth is the division of one bacterium into two daughter cells in a process called binary fission. Providing no mutational event occurs the resulting daughter cells are genetically identical to the original cell. Therefore, “local doubling” of the bacterial population occurs. Both daughter cells from the division do not necessarily survive. The doubling time is the generation time of the bacteria. If the number surviving exceeds unity on average, the bacterial population undergoes exponential growth.

The measurement of an exponential bacterial growth curve in batch culture was traditionally a part of the training of all microbiologists. The basic means requires bacterial enumeration (cell counting) by direct and individual (microscopic, flow cytometry), direct and bulk (biomass), indirect and individual (colony counting), or indirect and bulk (most probable number, turbidity, nutrient uptake) methods. In autecological studies, bacterial growth in batch culture can be modeled with four different phases: lag phase, exponential or log phase, stationary phase, and death phase.

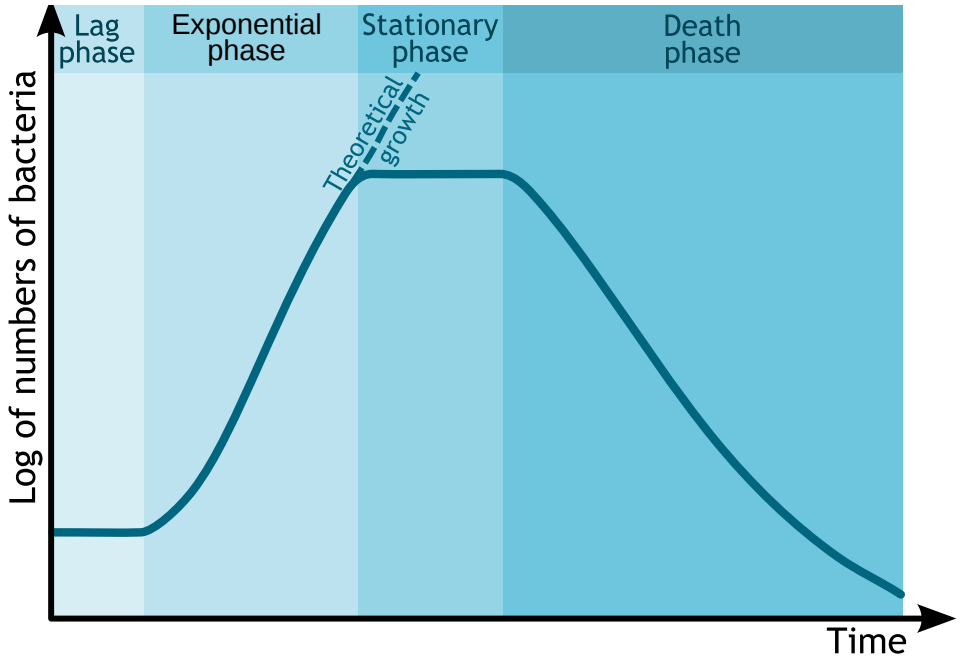

Figure: ***Bacterial Growth Curve****: This chart shows the logarithmic growth of bacteria. Note the Y-axis scale is logarithmic meaning that the number represents doubling. The phases of growth are labelled on top.*

During lag phase, bacteria adapt themselves to growth conditions. It is the period where the individual bacteria are maturing and not yet able to divide. During this phase of the bacterial growth cycle, synthesis of RNA, enzymes, and other molecules occurs. The exponential phase (sometimes called the log phase or the logarithmic phase) is a period characterized by cell doubling. The number of new bacteria appearing per unit time is proportional to the present population. If growth is not limited, doubling will continue at a constant rate so both the number of cells and the rate of population increase doubles with each consecutive time period. For this type of exponential growth, plotting the natural logarithm of cell number against time produces a straight line. The slope of this line is the specific growth rate of the organism, which is a measure of the number of divisions per cell per unit time.

The actual rate of this growth (i.e. the slope of the line in the figure) depends upon the growth conditions, which affect the frequency of cell division events and the probability of both daughter cells surviving. However, exponential growth cannot continue indefinitely because the medium is soon depleted of nutrients and enriched with wastes. Finally, the stationary phase is due to a growth-limiting factor, such as depletion of a nutrient and/or the formation of inhibitory products such as organic acids. Death of cells as a function of time is rather unpredictable and very difficult to explain. At death phase, bacteria run out of nutrients and die. This basic batch culture growth model draws out and emphasizes aspects of bacterial growth which may differ from the growth of macrofauna. It emphasizes clonality, asexual binary division, the short development time relative to replication itself, the

seemingly low death rate, the need to move from a dormant state to a reproductive state or to condition the media, and finally, the tendency of lab adapted strains to exhaust their nutrients. In reality, even in batch culture, the four phases are not well defined.

Key Points

- The doubling time is the generation time of the bacteria.
- The measurement of an exponential bacterial growth curve can be done by cell counting, colony counting, or determining the turbidity of bacterial cultures.
- Bacterial growth in batch culture can be modeled with four different phases: lag phase, exponential or log phase, stationary phase, and death phase.

Key Terms

- **bacterium**: A single celled organism with no nucleus.
- **bacterial growth**: Bacterial growth is the division of one bacterium into two daughter cells in a process called binary fission.
- **doubling time**: The doubling time is the period of time required for a quantity to double in size or value. It is applied to population growth, inflation, resource extraction, consumption of goods, compound interest, the volume of malignant tumours, and many other things which tend to grow over time.
- **lag phase**: the period of bacterial growth in which bacteria adapt themselves to growth conditions; the individual bacteria are maturing and not yet able to divide
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SECTION OVERVIEW

6.7: Bacterial Population Growth

Topic hierarchy

6.7A: Microbial Growth Cycle

6.7B: Growth Terminology

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6.7A: Microbial Growth Cycle

Increases in cell size are tightly linked in unicellular organisms and under optimal conditions bacteria can grow and divide rapidly.

LEARNING OBJECTIVES

Duplicate the requirements of microbial growth cycles

Key Takeaways

Key Points

- Bacteria grow to a fixed size and then reproduce through binary fission which a form of asexual reproduction. Under optimal conditions, bacteria can grow and divide extremely rapidly.
- Different kinds of bacteria need different amounts of oxygen to survive.
- For microbial growth to process, microorganisms require certain nutrients including carbon, nitrogen, phosphorus, sulfur, and metal ions.
- Various types of bacteria thrive at different temperatures.

Key Terms

- **binary fission**: The process whereby a cell divides asexually to produce two daughter cells.
- **Anaerobe**: An anaerobic organism; one that does not require oxygen to sustain its metabolic processes.
- **Aerobe**: Any organism (but especially a bacterium) that can tolerate the presence of oxygen or that needs oxygen to survive.

Microbial Growth Cycle

All microbial metabolisms can be arranged according to three principles: 1) How the organism obtains carbon for synthesizing cell mass. 2) How the organism obtains reducing equivalents used either in energy conservation or in biosynthetic reactions. 3) How the organism obtains energy for living and growing (for more detail on this topic see atom on Growth Terminology). Unlike in multicellular organisms, increases in cell size (cell growth and reproduction by cell division) are tightly linked in unicellular organisms. Bacteria grow to a fixed size and then reproduce through binary fission which is a form of asexual reproduction. Under optimal conditions, bacteria can grow and divide extremely rapidly. These optimal conditions are discussed below.

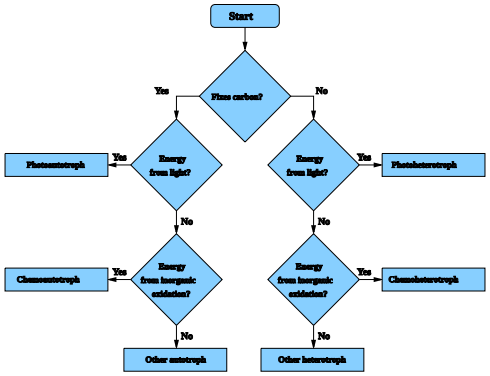

Figure: **Metabolic characteristics of microorganisms**: This is a flowchart to help determine how a microorganism undergoes growth development.

Oxygen Requirements

Different kinds of bacteria need different amounts of oxygen to survive, which determines which bacteria can infect which parts of the body. They are not able infect the skin because oxygen is present, and they can only grow in the presence of oxygen. Conversely, obligate anaerobes are killed by oxygen and carry out fermentation. Tetanus is an obligate anaerobe so it will infect areas where oxygen in limited. Aerotolerant anaerobes breath anaerobically (without oxygen), but they are able to survive when oxygen is present.

Nutrient Requirements

For microbial growth to process, microorganisms require certain nutrients including carbon, nitrogen, phosphorus, sulfur, and metal ions.

Temperature Requirements

Various types of bacteria thrive at different temperatures. Microorganisms that grow best at moderate temperatures are called mesophiles. Those surviving at high temperatures are thermophiles and microorganisms surviving at very low temperatures are called psychrophiles.

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6.7B: Growth Terminology

The two ways that microbial organisms can be classified are as autotrophs (supply their own energy) or as heterotrophs (use the products of others).

LEARNING OBJECTIVES

Recall bacterial growth terminology

Key Takeaways

Key Points

- An autotroph, which means self-feeding or producer, is an organism that produces complex organic compounds (such as carbohydrates and proteins) from simple substances present in its surroundings. To produce these organic compounds it either uses energy from light or inorganic chemical reactions.
- Photoautotrophs are a type of autotroph that use light (sunlight if they are green plants) as their energy source.
- Chemoautotrophs are also a type of autotroph that derive energy from chemical reactions and synthesize all necessary organic compounds from carbon dioxide.
- A heterotroph is an organism that, unlike an autotroph, cannot fix carbon and uses organic carbon for growth. Heterotrophs use the products formed by autotrophs to survive.
- Photoheterotrophs are a type of heterotroph that use light for energy, but cannot use carbon dioxide as their sole carbon source.
- Chemoheterotrophs are a type of heterotroph that are unable to fix carbon and form their own organic compounds so they must use products formed by autotrophs.

Key Terms

- **autotroph**: an organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **heterotroph**: An organism which requires an external supply of energy in the form of food as it cannot synthesize its own.

Growth Terminology

The two ways that microbial organisms can be classified are as autotrophs (supply their own energy) or as heterotrophs (use the products of others).

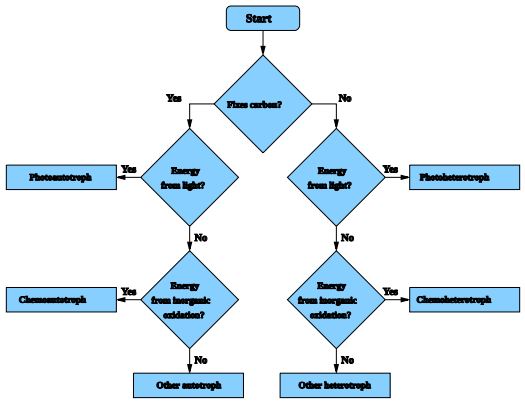

Figure: **Metabolic characteristics of microorganisms**: This is a flowchart to help determine how a microorganism undergoes growth development.

Autotrophs

An autotroph, which means self-feeding or producer, is an organism that produces complex organic compounds (such as carbohydrates, fats, and proteins) from simple substances present in its surroundings. To produce these organic compounds it either uses energy from light (by photosynthesis) or inorganic chemical reactions. Autotrophs reduce carbon dioxide (CO_2) by adding hydrogen atoms to it. This reduction process forms an organic compound that stores chemical energy. Most autotrophs use water as their reducing agent (to gain hydrogen atoms), but some can use other hydrogen compounds like hydrogen sulfide. Autotrophs, and

their formation of organic compounds, are an important component of the food chain because they produce the food necessary for larger, more complex organisms to grow.

Photoautotrophs

Photoautotrophs are a type of autotroph. Photoautotrophs use light (sunlight if they are green plants) as their energy source. They use this energy (physical) and convert it into chemical energy in the form of reduced carbon. This process produces energy that carries out various cellular metabolic processes.

Chemoautotrophs

Chemoautotrophs are also a type of autotroph. They derive their energy from chemical reactions and synthesize all necessary organic compounds from carbon dioxide. Most chemoautotrophs are bacteria and archaea that live in hostile environments (such as deep sea vents). Chemoautotrophs are thought to be the first organisms to inhabit earth.

Heterotrophs

A heterotroph is an organism that, unlike an autotroph, cannot fix carbon and uses organic carbon for growth. Heterotrophs use the products formed by autotrophs to survive.

Photoheterotrophs

Photoheterotrophs are a type of heterotroph. These organisms use light for energy, but cannot use carbon dioxide as their sole carbon source. They use compounds formed by autotrophs (such as carbohydrates, fatty acids, and alcohols) as their food.

Chemoheterotrophs

Chemoheterotrophs are a type of heterotroph. They are unable to fix carbon and form their own organic compounds so they must use products formed by autotrophs. These organisms use inorganic energy sources or organic energy sources to sustain life.

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SECTION OVERVIEW

6.8: Counting Bacteria

Topic hierarchy

6.8A: Direct Counting

6.8B: Viable Cell Counting

6.8C: Measurements of Microbial Mass

6.8D: Detecting Acid and Gas Production

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6.8A: Direct Counting

Learning Objectives

- Contrast ways of directly counting bacteria

Numerous procedures in biology and medicine require that cells be counted. On almost all occasions, what gets counted is actually the concentration of the cells (for example: 5,000 cells per milliliter). By counting the cells in a known volume of a culture, the concentration can be assessed. In medicine, the concentration of various blood cells, such as red blood cells or white blood cells, can give crucial information regarding someone's health. Similarly, the concentration of bacteria, viruses, and other pathogens in blood or bodily fluids can reveal information about the progress of an infectious disease and about how a person's immune system is dealing with the infection. Knowing the cell concentration is important in molecular biology experiments in order to adjust the amount of reagents and chemicals applied to the experiment.

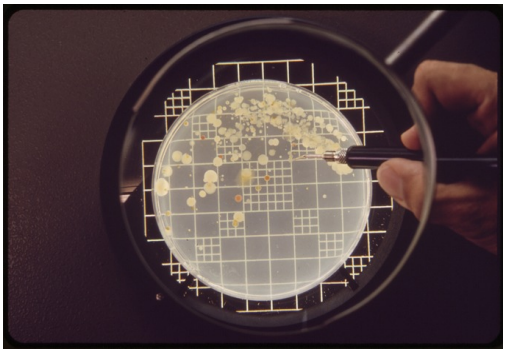

Figure: ***Counting Colonies****: An example of counting colonies on a streak plate.*

Direct counting methods include microscopic counts using a hemocytometer or a counting chamber. The hemocytometer works by creating a volumetric grid divided into differently sized cubes for accurately counting the number of particles in a cube and calculating the concentration of the entire sample. One can also quantify the number of cells in a culture by plating a known volume of the cell culture on a petri dish with a growth medium, which is also known as a streak plate. If the cells are distributed on the plate properly, it can generally be assumed that each cell will give rise to a single colony. The colonies can then be counted and, based on the known volume of the culture that was spread on the plate, the cell concentration can be calculated. Bacterial colony counts made from plating dilutions of bacteria are useful to estimate the strength of bacterial infections; for example, a urinary tract bacterial infection.

As with hemocytometers or counting chambers, cultures need to be heavily diluted prior to plating. Otherwise, instead of obtaining single colonies that can be counted, a so-called "lawn" of thousands of colonies will form, all lying atop each other. Additionally, plating is the slowest method because most microorganisms need at least 12 hours to form visible colonies. These methods of direct counting do not require sophisticated instrumentation, so they can easily be performed in most laboratories.

Key Points

- Directly counting blood cells or tissue cells by using a hemocytometer can determine the concentration of a known volume.
- Counting the number of colonies that arise on a pour plate can calculate the concentration by multiplying the count by the volume spread on the pour plate.
- Direct counting methods are easy to perform and do not require highly specialized equipment, but are often slower than other methods.

Key Terms

- **hemocytometer**: A device that counts microscopic particles. The hemocytometer works by creating a volumetric grid divided into differently sized cubes for accurately counting the number of particles in a cube and calculating the concentration of the entire sample.
- **streak plate**: A petri dish with a growth medium.

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6.8B: Viable Cell Counting

Plate counting is used to estimate the number of viable cells that are present in a sample.

LEARNING OBJECTIVES

Explain viable cell counting

Key Takeaways

Key Points

- The spread plate relies on bacteria growing a colony on a nutrient medium so that the colony becomes visible to the naked eye and the number of colonies on a plate can be counted.
- Selective media can be used to restrict the growth of non-target bacteria.
- The pour plate method is used when the analysis is looking for bacterial species that grow poorly in air, for example water samples.

Key Terms

- **plate count**: A means to identify the number of actively growing cells in a sample.

Viable Cell Counting

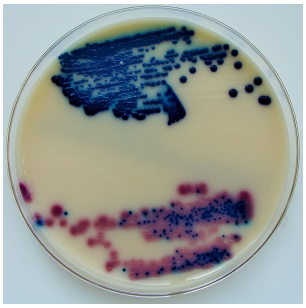

Figure: **Selective media can be used to restrict the growth of non-target bacteria.**: Urine cultured on Oxoid Brilliance UTI Agar plate. 1uL of urine spread onto the agar surface. The top sample is from patient with clinical urinary tract infection (UTI). The bottom sample is a mixed culture.

There are a variety of ways to enumerate the number of bacteria in a sample. A viable cell count allows one to identify the number of actively growing/dividing cells in a sample. The plate count method or spread plate relies on bacteria growing a colony on a nutrient medium. The colony becomes visible to the naked eye and the number of colonies on a plate can be counted. To be effective, the dilution of the original sample must be arranged so that on average between 30 and 300 colonies of the target bacterium are grown. Fewer than 30 colonies makes the interpretation statistically unsound and greater than 300 colonies often results in overlapping colonies and imprecision in the count. To ensure that an appropriate number of colonies will be generated several dilutions are normally cultured. The laboratory procedure involves making serial dilutions of the sample (1:10, 1:100, 1:1000 etc.) in sterile water and cultivating these on nutrient agar in a dish that is sealed and incubated. Typical media include Plate count agar for a general count or MacConkey agar to count gram-negative bacteria such as E. coli. Typically one set of plates is incubated at 22°C and for 24 hours and a second set at 37°C for 24 hours. The composition of the nutrient usually includes reagents that resist the growth of non-target organisms and make the target organism easily identified, often by a color change in the medium. Some recent methods include a fluorescent agent so that counting of the colonies can be automated. At the end of the incubation period the colonies are counted by eye, a procedure that takes a few moments and does not require a microscope as the colonies are typically a few millimeters across.

The pour plate method is used when the analysis is looking for bacterial species that grow poorly in air. The initial analysis is done by mixing serial dilutions of the sample in liquid nutrient agar which is then poured into bottles. The bottles are then sealed and laid on their sides to produce a sloping agar surface. Colonies that develop in the body of the medium can be counted by eye after incubation. The total number of colonies is referred to as the Total Viable Count (TVC). The unit of measurement is cfu/ml (or colony forming units per milliliter) and relates to the original sample. Calculation of this is a multiple of the counted number of colonies multiplied by the dilution used. Examples of a viable cell count are spread plates from a serial dilution of a liquid culture

and pour plates. With a spread plate one makes serial dilutions in liquid media and then spreads a known volume from the last tube in the dilution series. The colonies on the plate can then be counted and the concentration of bacteria in the original culture can be calculated. In the pour plate method a diluted bacterial sample is mixed with melted agar and then that mixture is poured into a petri dish. Again the colonies would be counted and the viable cell count calculated.

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6.8C: Measurements of Microbial Mass

Learning Objectives

- Recall ways of measuring microbial mass

Bacterial growth follows three phases: the lag phase, the log phase, and the stationary phase. The measurement of an exponential bacterial growth curve in a batch culture was traditionally a part of the training of all microbiologists; the basic means requires bacterial enumeration (cell counting) by direct and individual (microscopic, flow cytometry), direct and bulk (biomass), indirect and individual (colony counting), or indirect and bulk (most probable number, turbidity, nutrient uptake) methods. Models reconcile theory with the measurements.

METHODS OF MEASUREMENT

There are several methods for measuring cell mass, including the *gravimetermethod* which uses ordinary balances to weigh a sample (dry weight/ml) after the water has been removed.

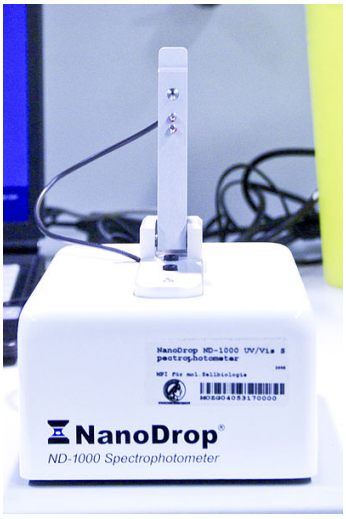

Figure: **Spectrophotometer**: This spectrophotometer can measure as little as one microliter of a sample.

An indirect method for calculating cell mass is *turbidimetry*. Cell cultures are turbid: they absorb some of the light and let the rest of it pass through. The higher the cell concentration is, the higher the turbidity. Spectrophotometers are electrical appliances that can measure turbidity very accurately. The culture is placed in a translucent cuvette; the cuvette is placed in the machine and the turbidity measured immediately. Simple mathematical formulae help convert the detected turbidity to cell concentration. Using spectrophotometry for measuring the turbidity of cultures is known as *turbidometry*. Note the difference in spelling: *turbidimetry* and *turbidometry* are not the same word.

In spectrophotometry, cultures usually do not need to be diluted, although above a certain cell density the results lose reliability. Of all the electrical appliances used for counting cells, a spectrophotometer is the cheapest and its operation the fastest and most straightforward. This has made spectrophotometry the methods of choice for quick measurements of bacterial growth and related applications. There are spectrophotometers in which several cuvettes can be inserted at one time, reducing work time even more. Additionally, there are spectrophotometers that require extremely small volumes of culture, as little as 1 microliter. This, combined with the stochastic nature of liquid cultures, enables only an estimation of cell numbers.

An additional method for the measurement of microbial mass is the quantification of cells in a culture by *plating the cells on a petri dish*. If the cells are efficiently distributed on the plate, it can be generally assumed that each cell will give rise to a single colony. The colonies can then be counted, and based on the known volume of culture that was spread on the plate the cell concentration can be calculated.

As is with counting chambers, cultures usually need to be heavily diluted prior to plating; otherwise, instead of obtaining single colonies that can be counted, a so-called “lawn” will form, resulting in thousands of colonies lying over each other. Additionally, plating is the slowest method of all: most microorganisms need at least 12 hours to form visible colonies.

Key Points

- Calculating the dry weight of a sample enables one to calculate the cell count, but the sensitivity is limited to samples containing more than 10E8 bacteria per milliliter.
- Spectrophotometry is an indirect method for calculating cell concentrations by measuring the changes in turbidity.
- Bacteria can also be counted by using the plating method, which is based on the number of colonies formed in Petri dishes containing specific growth media.

Key Terms

- **spectrophotometry**: A spectrophotometer is commonly used for the measurement of transmittance or reflectance of solutions. However they can also be designed to measure the diffusivity on any of the listed light ranges that usually cover around 200nm – 2500nm using different controls and calibrations. [2] Within these ranges of light, calibrations are needed on the machine using standards that vary in type depending on the wavelength of the photometric determination. [3]
- **flow cytometry**: A technique used to sort and classify cells by using fluorescent markers on their surface.
- **gravimeter**: An instrument used to measure local variations in the gravitational field

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6.8D: Detecting Acid and Gas Production

Culture media can be used to differentiate between different kinds of bacteria by detecting acid or gas production.

LEARNING OBJECTIVES

Show how microbial acid and gas production are detected

Key Takeaways

Key Points

- Differential media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators.
- To measure acid production one can use a pH indicator in the media.
- The Durham tube method is used to detect production of gas by microorganisms.

Key Terms

- **differential media**: Differential media or indicator media distinguish one microorganism type from another growing on the same media.

Cultures and Differential Media

A microbiological culture, or microbial culture, is created using a method for multiplying microbial organisms by letting them reproduce in predetermined culture media under controlled laboratory conditions. Microbial cultures are used to determine an organism's type, its abundance in the sample being tested, or both. It is one of the primary diagnostic techniques of microbiology, where it is used as a tool to determine the cause of infectious diseases by letting the agent multiply in a predetermined medium. A throat culture, for example, is taken by scraping the lining of tissue in the back of the throat and blotting the sample into a growing medium; this will allow analysis to screen for harmful microorganisms, such as *Streptococcus pyogenes*, the causative agent of strep throat. The term "culture" can be used to refer to the process of culturing organisms, to the medium they're grown in, and is more generally used informally to refer to "selectively growing" a specific kind of microorganism in the lab.

Differential media, also known as indicator media, distinguish one microorganism type from another growing on the same media. These types of media use the biochemical characteristics of a microorganism grown in the presence of specific nutrients or indicators that have been added to the medium to visibly indicate the defining characteristics of a microorganism. These indicators or nutrients include but are not limited to neutral red, phenol red, eosin y, and methylene blue. Differential media are used for the detection of microorganisms and by molecular biologists to detect recombinant strains of bacteria.

Durham Cultures

The Durham tube method is used to detect production of gas by microorganisms. They are simply smaller test tubes inserted upside down in another test tube. This small tube is initially filled with the solution in which the microorganism is to be grown. If gas is produced after inoculation and incubation, a visible gas bubble will be trapped inside the small tube. The initial air gap produced when the tube is inserted upside down is lost during sterilization, usually performed at 121°C for 15 or so minutes

Escherichia coli

Escherichia coli (*E. coli*), a rod-shaped member of the coliform group, can be distinguished from most other coliforms by its ability to ferment lactose at 44°C in the fecal coliform test, and by its growth and color reaction on certain types of culture media. When cultured on an EMB (eosin methylene blue) plate, a positive result for *E. coli* is metallic green colonies on a dark purple media. Unlike the general coliform group, *E. coli* are almost exclusively of fecal origin and their presence is thus an effective confirmation of fecal contamination. Some strains of *E. coli* can cause serious illness in humans.

Sorbitol MacConkey Agar

Sorbitol MacConkey agar is a variant of the traditional MacConkey commonly used in the detection of *E. coli* O157:H7. Traditionally, MacConkey agar has been used to distinguish those bacteria that ferment lactose from those that do not.

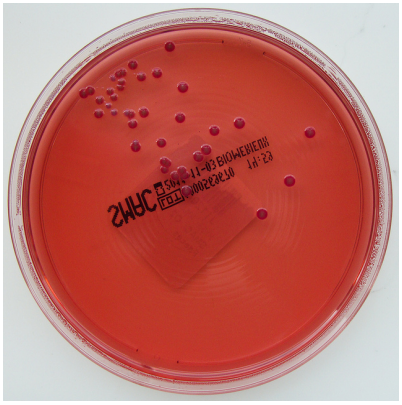

Figure: **Using differential media to detect acid production**: Sorbitol fermenting non pathogenic commensal bacteria from faeces growing on Cefixime Tellurite Sorbitol MacConkey Agar.

This is an important distinction. Gut bacteria, such as *Escherichia coli*, can typically ferment lactose; important gut pathogens including *Salmonella enterica* and most *shigellas* are unable to ferment lactose. *Shigella sonnei* can ferment lactose, but only after prolonged incubation; it is referred to as a *late-lactose fermenter*.

During fermentation of sugar, acid is formed and the pH of the medium drops, changing the color of the pH indicator. Different formulations use different indicators; neutral red is often used when culturing gut bacteria because lactose fermenters turn a deep red when this pH indicator is used. Those bacteria unable to ferment lactose, often referred to as *nonlactose fermenters* (NLFs) metabolize the peptone in the medium. This releases ammonia, which raises the pH of the medium. Although some authors refer to NLFs as being colorless, in reality they turn neutral red a buffish color.

E. coli O157:H7 differs from most other strains of *E. coli* in being unable to ferment sorbitol. In sorbitol MacConkey agar, lactose is replaced by sorbitol. Most strains of *E. coli* ferment sorbitol to produce acid: *E. coli* O157:H7 can not ferment sorbitol, so this strain uses peptone to grow. This raises the pH of the medium, allowing the O157:H7 strain to be differentiated from other *E. coli* strains through the action of the pH indicator in the medium.

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SECTION OVERVIEW

6.9: Temperature and Microbial Growth

Topic hierarchy

6.9A: Growth Rate and Temperature

6.9B: Classification of Microorganisms by Growth Temperature

6.9C: The Heat-Shock Response

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6.9A: Growth Rate and Temperature

Bacteria may grow across a wide range of temperatures, from very cold to very hot.

LEARNING OBJECTIVES

Describe how the growth of bacteria is affected by temperature and how bacterial growth can be measured

Key Takeaways

Key Points

- The basic means of measuring growth requires bacterial enumeration (cell counting).
- Methods for bacterial cell counting include: 1. direct and individual (microscopic, flow cytometry), 2. direct and bulk (biomass), 3. indirect and individual (colony counting), or 4. indirect and bulk (most probable number, turbidity, nutrient uptake).
- A mesophile is an organism that grows best in moderate temperature, neither too hot nor too cold. All human pathogens are mesophiles.
- Cold shock proteins help the cell to survive in temperatures lower than optimum growth temperature.
- Heat shock proteins help the cell to survive in temperatures greater than the optimum, possibly by condensation of the chromosome and organization of the prokaryotic nucleoid.

Key Terms

- **mesophile**: An organism, especially a microorganism, that lives and thrives at moderate temperatures.
- **psychrophile**: An organism that can live and thrive at temperatures much lower than normal; a form of extremophile.
- **thermophile**: An organism that lives and thrives at relatively high temperatures; a form of extremophile; many are members of the Archaea.

Growth Rate and Temperature

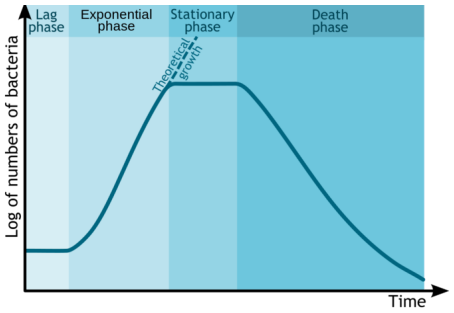

Figure: **Bacterial growth curve**: Bacterial growth in batch culture can be modeled with four different phases: (A) the lag phase, when the population stays roughly the same; (B) the exponential, or log, phase, when the population grows at an increasing rate; (C) the stationary phase, when population growth stagnates; and (D) the death phase, when bacteria begin to die off and the population decreases in size.

Bacterial growth is the division of one bacterium into two daughter cells in a process called binary fission. Providing no mutational event occurs the resulting daughter cells are genetically identical to the original cell. Hence, local doubling of the bacterial population occurs. Both daughter cells from the division do not necessarily survive. However, if the number surviving exceeds unity on average, the bacterial population undergoes exponential growth. The measurement of an exponential bacterial growth curve in batch culture was traditionally a part of the training of all microbiologists. The basic means requires bacterial enumeration (cell counting) by direct and individual (microscopic, flow cytometry), direct and bulk (biomass), indirect and individual (colony counting), or indirect and bulk (most probable number, turbidity, nutrient uptake) methods. Models reconcile theory with the measurements.



Figure: **Grand Prismatic Spring, Midway & Lower Geyser Basin, Yellowstone National Park**: This photo shows steam rising from hot and sterile deep azure blue water in the center, surrounded by huge mats of brilliant orange algae, bacteria and archaea. These colorful microorganisms are called extremophiles—these in particular are thermophiles.

Bacteria may grow across a wide range of temperatures, from very cold to very hot. A mesophile is an organism that grows best in moderate temperature, neither too hot nor too cold. All human pathogens are mesophiles. Organisms that prefer extreme environments are known as extremophiles: those that prefer cold environments are termed psychrophilic, those preferring warmer temperatures are termed thermophilic or thermotrophs and those thriving in extremely hot environments are hyperthermophilic.

For example, in molecular biology, the cold-shock domain (CSD) is a protein domain of about 70 amino acids which has been found in prokaryotic and eukaryotic DNA-binding proteins. Part of this domain is highly similar to the RNP-1 RNA-binding motif. When Escherichia coli is exposed to a temperature drop from 37 to 10 degrees Celsius, a four to five hour lag phase occurs and then growth is resumed at a reduced rate. During the lag phase, the expression of around 13 proteins, which contain cold shock domains is increased two- to ten-fold. These so-called cold shock proteins are thought to help the cell survive in temperatures lower than optimum growth temperature, by contrast with heat shock proteins, which help the cell survive in temperatures greater than the optimum, possibly by condensation of the chromosome and organization of the prokaryotic nucleoid.

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6.9B: Classification of Microorganisms by Growth Temperature

Bacteria can be classified on the basis of cell structure, metabolism or on differences in cell components.

LEARNING OBJECTIVES

Describe how bacteria can be classified on the basis of cell structure, cellular metabolism or differences in cell components such as DNA

Key Takeaways

Key Points

- A mesophile is an organism that grows best in moderate temperature, neither too hot nor too cold, typically between 20 and 45 °C (68 and 113 °F).The term is mainly applied to microorganisms.
- All bacteria have their own optimum environmental surroundings and temperatures in which they thrive the most.
- Thermophiles contain enzymes that can function at high temperatures. Some of these enzymes are used in molecular biology (for example, heat-stable DNA polymerases for PCR), and in washing agents.

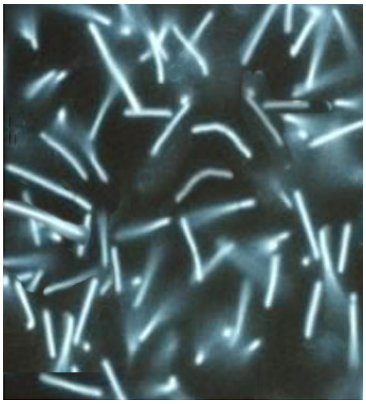
Key Terms

- **mesophile**: An organism, especially a microorganism, that lives and thrives at moderate temperatures.
- **thermophile**: An organism that lives and thrives at relatively high temperatures; a form of extremophile; many are members of the Archaea.

Classification seeks to describe the diversity of bacterial species by naming and grouping organisms based on similarities. Bacteria can be classified on the basis of cell structure, cellular metabolism, or on differences in cell components such as DNA, fatty acids, pigments, antigens and quinones.

Bacteria can be classified by their optimal growth temperature. The following are the five classifications:

- Hyperthermophile (60 degrees C and upwards)
- Thermophile (optimal growth between 45 and 122 degrees)
- Mesophile (20 and 45 degrees C)
- Psychrotrophs (will survive at 0 degrees C, but prefer mesophilic temperature
- Psychrophiles (-15 and 10 degrees C or lower)



Methanopyrus kandleri

Methanopyrus kandleri can survive and reproduce at 122 °C.

A mesophile is an organism that grows best in moderate temperature, neither too hot nor too cold, typically between 20 and 45 °C (68 and 113 °F). The term is mainly applied to microorganisms.The habitats of these organisms include especially cheese, yogurt, and mesophile organisms are often included in the process of beer and wine making. Organisms that prefer cold environments are termed psychrophilic, those preferring warmer temperatures are termed thermophilic and those thriving in extremely hot environments are hyperthermophilic. All bacteria have their own optimum environmental surroundings and temperatures in which

they thrive the most. A thermophile is an organism — a type of extremophile — that thrives at relatively high temperatures, between 45 and 122 °C (113 and 252 °F). Thermophilic eubacteria are suggested to have been among the earliest bacteria. Thermophiles are found in various geothermally heated regions of the Earth, such as hot springs like those in Yellowstone National Park. and deep sea hydrothermal vents, as well as decaying plant matter, such as peat bogs and compost.As a prerequisite for their survival, thermophiles contain enzymes that can function at high temperatures. Some of these enzymes are used in molecular biology (for example, heat-stable DNA polymerases for PCR), and in washing agents.

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6.9C: The Heat-Shock Response

Heat shock response is a cell's response to intense heat, including up-regulation of heat shock proteins.

LEARNING OBJECTIVES

Describe how the bacterial stress response enables bacteria to survive adverse and fluctuating conditions in their immediate surroundings such as increases in temperature

Key Takeaways

Key Points

- The bacterial stress response enables bacteria to survive adverse and fluctuating conditions in their immediate surroundings.
- A bacterial cell can react simultaneously to a wide variety of stresses and the various stress response systems interact with each other by a complex of global regulatory networks.
- The up-regulation of HSPs during heat shock is generally controlled by a single transcription factor; in eukaryotes this regulation is performed by heat shock factor (HSF), while σ32 is the heat shock sigma factor in Escherichia coli.

Key Terms

- **heat shock response**: The cellular response to heat shock.

The bacterial stress response enables bacteria to survive adverse and fluctuating conditions in their immediate surroundings. Various bacterial mechanisms recognize different environmental changes and mount an appropriate response. A bacterial cell can react simultaneously to a wide variety of stresses, and the various stress response systems interact with each other by a complex of global regulatory networks.

In biochemistry, heat shock is the "effect of subjecting a cell to a higher temperature than that of the ideal body temperature of the organism from which the cell line was derived. "

Heat shock response is the cellular response to heat shock includes the transcriptional up-regulation of genes encoding heat shock proteins (HSPs) as part of the cell's internal repair mechanism. HSPs are also called 'stress-proteins' and respond to heat, cold and oxygen deprivation by activating several cascade pathways. HSPs are also present in cells under perfectly normal conditions. Some HSPs, called 'chaperones', ensure that the cell's proteins are in the right shape and in the right place at the right time. For example, HSPs help new or misfolded proteins to fold into their correct three-dimensional conformations, which is essential for their function. They also shuttle proteins from one compartment to another inside the cell and target old or terminally misfolded proteins to proteases for degradation. Additionally, heat shock proteins are believed to play a role in the presentation of pieces of proteins (or peptides) on the cell surface to help the immune system recognize diseased cells. The up-regulation of HSPs during heat shock is generally controlled by a single transcription factor; in eukaryotes this regulation is performed by heat shock factor (HSF), while σ32 is the heat shock sigma factor in Escherichia coli.

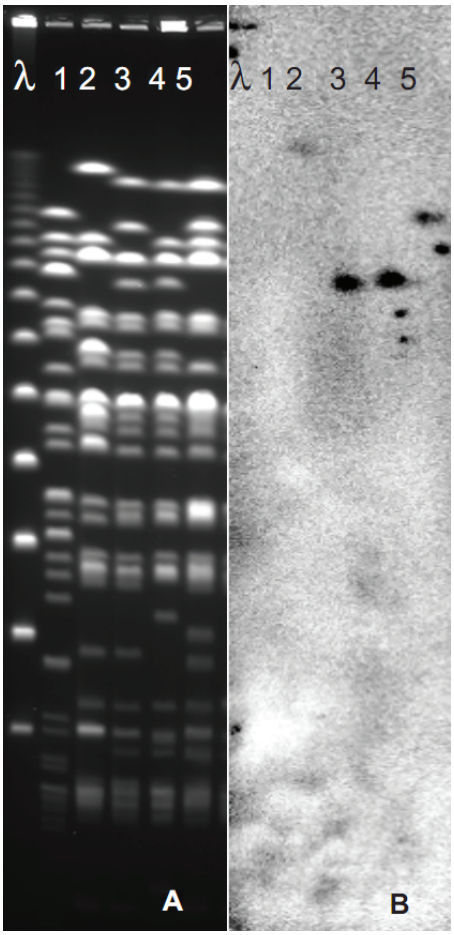

Figure: **Heat shock proteins**: Heat shock protein come in many sizes. This is an example of small heat shock proteins produced by Pseudomonas aeruginosa Clonal Variants Isolated from Diverse Niches.

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SECTION OVERVIEW

6. 10: Other Environmental Growth Factors

Topic hierarchy

6.10A: Gas Requirements

6.10B: Osmotic Pressure

6.10C: Microbial Growth at Low or High pH

6.10D: Oxygen

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6.10A: Gas Requirements

Cells are grown and maintained at an appropriate temperature and gas mixture of oxygen, carbon dioxide, and nitrogen in a cell incubator.

LEARNING OBJECTIVES

Compare different gas requirements of various microbes

Key Takeaways

Key Points

- Culture conditions vary greatly for each cell type. The variation of conditions for a particular cell type can result in different phenotypes.
- Capnophiles are microorganisms that thrive in the presence of high concentrations of carbon dioxide.
- Diazotrophs are microorganisms that fix atmospheric nitrogen gas into a more usable form such as ammonia.

Key Terms

- **capnophile**: A microorganism that requires or grows best in presence of high concentrations of carbon dioxide.
- **diazotroph**: A microorganism that can fix nitrogen.

Cells are grown and maintained at an appropriate temperature and gas mixture (typically, 37°C and a mixture of oxygen, carbon dioxide, and nitrogen) in a cell incubator. Culture conditions vary greatly for each cell type. The variation of conditions for a particular cell type can result in different phenotypes.



Figure: **Bacteriological incubator**: Cells are grown and maintained at an appropriate temperature and gas mixture of oxygen, carbon dioxide, and nitrogen in a cell incubator.

Capnophiles are microorganisms that thrive in the presence of high concentrations of carbon dioxide. Typically, in a cell culture the CO_2 concentration is around 5%. Some capnophiles may have a metabolic requirement for carbon dioxide, while others merely compete more successfully for resources under these conditions.

Diazotrophs are microorganisms that fix atmospheric nitrogen gas into a more usable form such as ammonia. A diazotroph is an organism that is able to grow without external sources of fixed nitrogen. Some example free-living diazotrophs include:

1) obligate anaerobes that cannot tolerate oxygen even if they are not fixing nitrogen. They live in habitats low in oxygen, such as soils and decaying vegetable matter.

2) Facultative anaerobes that can grow either with or without oxygen, but they only fix nitrogen anaerobically. Often, they respire oxygen as rapidly as it is supplied, keeping the amount of free oxygen low.

3) Aerobes that require oxygen to grow, yet their nitrogenase is still debilitated if exposed to oxygen.

4) Oxygenic photosynthetic bacteria generate oxygen as a by-product of photosynthesis, yet some are able to fix nitrogen as well.

5) And finally, Anoxygenic photosynthetic bacteria that do not generate oxygen during photosynthesis as they have only a single photosystem which cannot split water. In addition, nitrogenase is expressed under nitrogen limitation.

Some higher plants, and some animals (termites), have formed associations (symbioses) with diazotrophs. Examples of those diazotrophs include: rhizobia that associate with legumes, plants of the Fabaceae family, frankias, and cyanobacteria that associate

with fungi as lichens, with liverworts, with a fern, and with a cycad.

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6.10B: Osmotic Pressure

The correct osmotic pressure in the culture medium is essential for the survival of the cells.

LEARNING OBJECTIVES

Describe osmotic effects

Key Takeaways

Key Points

- Osmosis is the net movement of solvent molecules through a partially permeable membrane into a region of higher solute concentration in order to equalize the solute concentrations on the two sides.
- Osmosis provides the primary means by which water is transported into and out of cells.
- Osmoregulation is the homeostasis mechanism of an organism to reach balance in osmotic pressure.
- If the medium is hypotonic, the cells will gain water through osmosis.
- If the medium is hypertonic, the cells will lose water through osmosis.

Key Terms

- **osmosis**: the net movement of solvent molecules from a region of high solvent potential to a region of lower solvent potential through a partially permeable membrane
- **hypotonic**: Having a lower osmotic pressure than another.
- **isotonic**: Having the same osmotic pressure.
- **hypertonic**: Having a greater osmotic pressure than another.
- **halophile**: Organisms that thrive in high salt concentrations.

Osmotic pressure is an important factor that affects cells. Osmosis is the net movement of solvent molecules through a partially permeable membrane into a region of higher solute concentration. The intent of osmosis is to equalize the solute concentrations on the two sides. Osmosis is essential in biological systems because biological membranes are semi permeable. In general, these membranes are impermeable to large and polar molecules such as ions, proteins, and polysaccharides. However, they are permeable to non-polar and/or hydrophobic molecules like lipids as well as to small molecules like oxygen, carbon dioxide, nitrogen, nitric oxide, etc. Osmosis provides the primary means by which water is transported into and out of cells. Osmoregulation is the homeostasis mechanism of an organism to reach balance in osmotic pressure.

Having the correct osmotic pressure in the culture medium is essential. A cell can be influenced by a solution in three ways. Suppose a cell is placed in a solution of sugar or salt water. If the medium is hypotonic — a diluted solution with a higher water concentration than the cell — the cell will gain water through osmosis. If the medium is isotonic — a solution with exactly the same water concentration as the cell — there will be no net movement of water across the cell membrane. If the medium is hypertonic — a concentrated solution with a lower water concentration than the cell — the cell will lose water by osmosis.

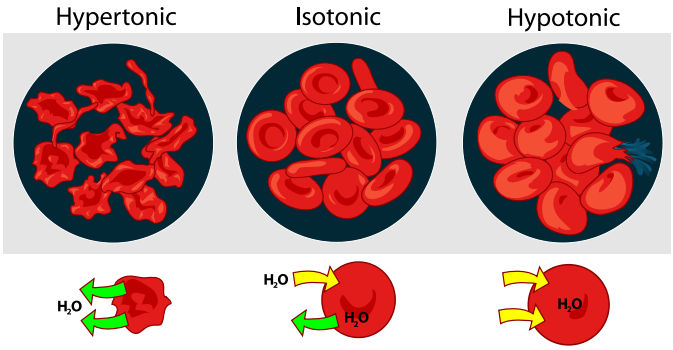

Figure: **Osmotic Pressure on Red Blood Cells**: Effect of different solutions on blood cells.

Essentially, this means that if a cell is put in a solution that has a solute concentration higher than its own, then it will shrivel up. If it is put in a solution with a lower solute concentration than its own, the cell will expand and burst.

Obligate and Facultative Halophiles

A halophile is a microorganism that can survive and replicate in a high salt concentration environment (high osmotic pressure).

Obligate halophiles are microorganisms that can only survive in high salt concentration environments. Facultative halophiles are able to survive in *both* high and normal salt concentration environments.

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6.10C: Microbial Growth at Low or High pH

Microorganisms live and thrive within specific pH levels.

LEARNING OBJECTIVES

Differentiate microbial growth at high or low pHs

Key Takeaways

Key Points

- Neutrophiles are organisms that thrive in neutral (pH 7) environments.
- Alkaliphiles are microbes that thrive in alkaline (pH 9-11) environments.
- Acidophilic organisms are those that thrive under highly acidic conditions (usually at pH 2.0 or below).

Key Terms

- **neutrophile**: any organism that thrives in a relatively neutral pH
- **alkaliphile**: any organism that lives and thrives in an alkaline environment, such as a soda lake; a form of extremophile
- **acidophile**: an organism that lives and thrives under acidic conditions; a form of extremophile

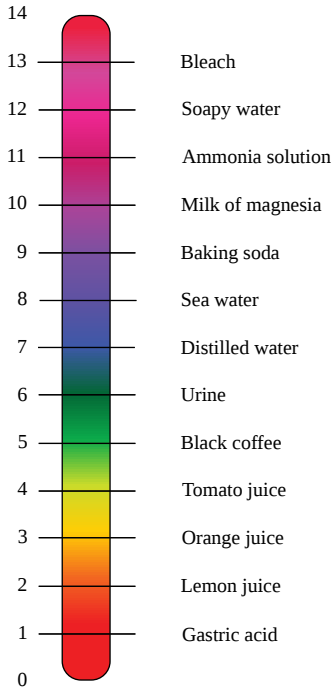

Figure: **pH scale**: A pH scale with annotated examples of chemicals at each integer pH value

In chemistry, pH is a measure of the activity of the (solvated) hydrogen ion. In other words, it is a measure of hydrogen ion concentration. Pure water has a pH very close to 7 at 25°C. Solutions with a pH less than 7 are said to be acidic, and solutions with a pH greater than 7 are said to be basic or alkaline. The pH scale is traceable to a set of standard solutions whose pH is established by international agreement. The pH of different cellular compartments, body fluids, and organs is usually tightly regulated in a process called acid-base homeostasis. Microorganisms live and thrive within specific pH levels.

Neutrophiles are organisms that thrive in neutral (pH 7) environments; extromophiles are organisms that thrive in extreme pH environments.

Alkaliphiles are microbes that thrive in alkaline environments with a pH of 9 to 11, such as playa lakes and carbonate-rich soils. To survive, alkaliphiles maintain a relatively low alkaline level of about 8 pH inside their cells by constantly pumping hydrogen ions in the form of hydronium ions (H3O+) across their cell membranes and into their cytoplasm.

Acidophilic organisms are those that thrive under highly acidic conditions (usually at pH 2.0 or below). Most acidophile organisms have evolved extremely efficient mechanisms to pump protons out of the intracellular space in order to keep the cytoplasm at or near neutral pH. Therefore, intracellular proteins do not need to develop acid stability through evolution. However, other acidophiles, such as Acetobacter aceti, have an acidified cytoplasm which forces nearly all proteins in the genome to evolve acid stability.

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6.10D: Oxygen

Oxygen requirements vary among microorganisms.

LEARNING OBJECTIVES

Identify the role of oxygen in microbial growth

Key Takeaways

Key Points

- An aerobic organism or aerobe is an organism that can survive and grow in an oxygenated environment.
- An anaerobic organism or anaerobe is any organism that does not require oxygen for growth.
- Normal microbial culturing occurs in an aerobic environment which poses a problem when culturing anaerobes; requiring one of a number of techniques to be used to keep oxygen out of the culturing setup.

Key Terms

- **anaerobic**: Without oxygen; especially of an environment or organism.
- **aerobic respiration**: metabolic reactions and processes that take place in the cells of organisms and require oxygen to convert biochemical energy from nutrients into adenosine triphosphate (ATP)
- **aerobic**: Living or occurring only in the presence of oxygen.
- **aerotolerant anaerobe**: an organism that does not require oxygen to sustain its metabolic processes, but is able to survive in the presence of oxygen

An aerobic organism or aerobe is an organism that can survive and grow in an oxygenated environment. Several varietis of aerobes exist. Obligate aerobes require oxygen for aerobic cellular respiration. In a process known as cellular respiration, these organisms use oxygen to oxidize substrates (for example sugars and fats) in order to obtain energy. Facultative anaerobes can use oxygen, but also have anaerobic (i.e. not requiring oxygen) methods of energy production. Microaerophiles are organisms that may use oxygen, but only at low concentrations. Aerotolerant organisms can survive in the presence of oxygen, but they are anaerobic because they do not use it as a terminal electron acceptor.

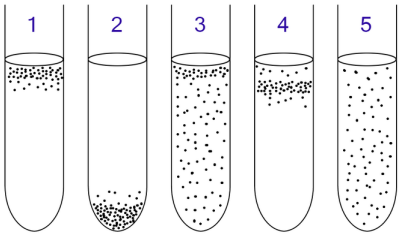

Figure: **Identity of aerobic and anaerobic bacteria**: Aerobically different bacteria behave differently when grown in liquid culture: 1) Obligate aerobic bacteria gather at the top of the test tube in order to absorb maximal amount of oxygen. 2) Obligate anaerobic bacteria gather at the bottom to avoid oxygen. 3) Facultative bacteria gather mostly at the top, since aerobic respiration is advantageous (ie, energetically favorable); but as lack of oxygen does not hurt them, they can be found all along the test tube. 4) Microaerophiles gather at the upper part of the test tube but not at the top. They require oxygen, but at a lower concentration. 5) Aerotolerant bacteria are not affected at all by oxygen, and they are evenly spread along the test tube.

An anaerobic organism or anaerobe is any organism that does not require oxygen for growth. It could possibly react negatively and may even die if oxygen is present. For practical purposes there are three categories: obligate anaerobes, which cannot use oxygen for growth and are even harmed by it. Aerotolerant organisms, which cannot use oxygen for growth, but tolerate the presence of it. And finally, facultative anaerobes, which can grow without oxygen but can utilize oxygen if it is present.

Since normal microbial culturing occurs in atmospheric air, which is an aerobic environment, the culturing of anaerobes poses a problem. Therefore, a number of techniques are employed by microbiologists when culturing anaerobic organisms, for example, handling the bacteria in a glovebox filled with nitrogen or the use of other specially-sealed containers.

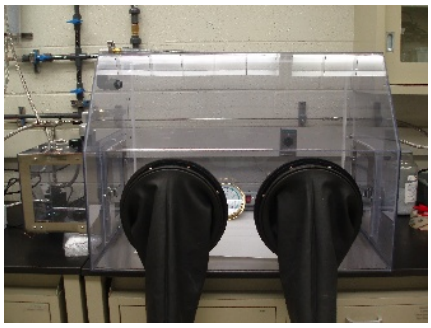

Figure: **Glovebox**: Terra Universal 100 Glovebox

The GasPak System is an isolated container that achieves an anaerobic environment by the reaction of water with sodium borohydride and sodium bicarbonate tablets to produce hydrogen gas and carbon dioxide. Hydrogen then reacts with oxygen gas on a palladium catalyst to produce more water, thereby removing oxygen gas.

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SECTION OVERVIEW

6. 11: Microbial Growth in Communities

Topic hierarchy

6.11A: Ecological Associations Among Microorganisms

6.11B: Biofilms

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6.11A: Ecological Associations Among Microorganisms

Despite an apparent simplicity, bacteria can form complex associations with other organisms.

LEARNING OBJECTIVES

Contrast the ecological associations among microorganisms

Key Takeaways

Key Points

- Due to their small size, commensal bacteria are ubiquitous and grow on animals and plants exactly as they would grow on any other surface. Their growth can be increased by warmth and sweat; in humans, large populations of these organisms are the cause of body odor.
- Pathogenic bacteria are a major cause of human death and disease, and cause infections such as tetanus, typhoid fever, diphtheria, syphilis, cholera, foodborne illness, leprosy and tuberculosis.
- Certain bacteria form mutualistic associations, such as close spatial associations that are essential for their survival; for example, interspecies hydrogen transfer.

Key Terms

- **mutualism**: Any interaction between two species that benefits both; typically involves the exchange of substances or services.
- **parasitism**: Interaction between two organisms, in which one organism (the parasite) benefits and the other (the host) is harmed.
- **commensalism**: Describes a relationship between two living organisms where one benefits and the other is not significantly harmed or helped.

Ecological Associations Among Microorganisms

Despite an apparent simplicity, bacteria can form complex associations with other organisms. This process is known as symbiosis. These symbiotic associations can be divided into parasitism, mutualism and commensalism. Due to their small size, commensal bacteria are ubiquitous and grow on animals and plants exactly as they would grow on any other surface. However, their growth can be increased by warmth and sweat; in humans, large populations of these organisms are the cause of body odor.

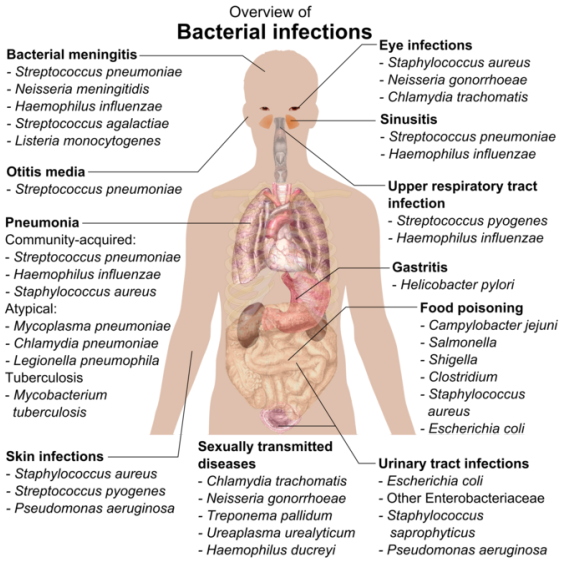

Figure: **Bacterial Infections in the Human Host**: Overview of the main bacterial infections and the most notable species involved

PREDATORS

Some species of bacteria kill and then consume other microorganisms; these species are called *predatory bacteria*. These include organisms such as*Myxococcus xanthus*, which forms swarms of cells that kill and digest any bacteria they encounter. Other

bacterial predators either attach to their prey in order to digest them and absorb nutrients, such as *Vampirococcus*, or invade another cell and multiply inside the cytosol, such as *Daptobacter*. These predatory bacteria are thought to have evolved from saprophages that consumed dead microorganisms through adaptations that allowed them to entrap and kill other organisms.

MUTUALISTS

Certain bacteria form close spatial associations that are essential for their survival. One such mutualistic association, called interspecies hydrogen transfer, occurs between clusters of anaerobic bacteria that consume organic acids, such as butyric acid or propionic acid, and produce hydrogen; and methanogenic Archaea, which consume hydrogen. The bacteria in this association are unable to consume the organic acids since this reaction produces hydrogen, which accumulates in the bacteria's surroundings. Only the intimate association with the hydrogen-consuming Archaea keeps the hydrogen concentration low enough to allow the bacteria to grow.

In soil, microorganisms that reside in the rhizospehere (a zone that includes the root surface and the soil that adheres to the root after gentle shaking) carry out nitrogen fixation, converting nitrogen gas to nitrogenous compound. This serves to provide an easily absorbable form of nitrogen for many plants that cannot fix nitrogen themselves. Many other bacteria are found as symbionts in humans and other organisms. For example, the presence of over one thousand bacterial species in the normal human gut flora of the intestines can contribute to gut immunity. Synthesis vitamins such as folic acid, vitamin K, and biotin convert sugars to lactic acid (see *Lactobacillus*), as well as fermenting complex undigestible carbohydrates. The presence of this gut flora also inhibits the growth of potentially pathogenic bacteria (usually through competitive exclusion), and these beneficial bacteria are consequently sold as probioticdietary supplements.

PATHOGENS

If bacteria form a parasitic association with other organisms, they are classed as pathogens. Pathogenic bacteria are a major cause of human death and disease and cause infections such as tetanus, typhoid fever, diphtheria, syphilis, cholera, foodborne illness, leprosy, and tuberculosis. A pathogenic cause for a known medical disease may only be discovered many years after, as was the case with *Helicobacter pylori* and peptic ulcer disease. Bacterial diseases are also important in agriculture, with bacteria causing leaf spot, fire blight, and wilts in plants; as well as Johne's disease, mastitis, salmonella, and anthrax in farm animals.

Each species of pathogen has a characteristic spectrum of interactions with its human hosts. Some organisms, such as *Staphylococcus or Streptococcus*, can cause skin infections, pneumonia, meningitis and even overwhelming sepsis, a systemic inflammatory response producing shock, massive vasodilation, and death. Yet these organisms are also part of the normal human flora and usually exist on the skin or in the nose without causing any disease at all. Other organisms invariably cause disease in humans, such as the *Rickettsia*, which are obligate intracellular parasites able to grow and reproduce only within the cells of other organisms. One species of *Rickettsia* causes typhus, while another causes Rocky Mountain spotted fever. *Chlamydia*, another phylum of obligate intracellular parasites, contains species that can cause pneumonia, or urinary tract infection and may be involved in coronary heart disease. Finally, some species such as *Pseudomonas aeruginosa*, *Burkholderia cenocepacia*, and *Mycobacterium avium* are opportunistic pathogens and cause disease mainly in people suffering from immunosuppression or cystic fibrosis.

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6.11B: Biofilms

Learning Objectives

- Describe biofilms

Biofilm is an aggregate of microorganisms in which cells adhere to each other on a surface. These cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS). Biofilm EPS, also referred to as slime, is a polymeric conglomeration composed of extracellular DNA, proteins, and polysaccharides. Biofilms may form on living or non-living surfaces and can be prevalent in natural, industrial, and hospital settings.

The microbial cells growing in a biofilm are physiologically distinct from planktonic cells of the same organism, which, by contrast, are single cells that may float or swim in liquid. Microbes form a biofilm in response to many factors, including cellular recognition of specific or non-specific attachment sites on a surface, nutritional cues, or exposure of planktonic cells to sub-inhibitory concentrations of antibiotics. When a cell switches to the biofilm mode of growth, it undergoes a phenotypic shift in behavior in which large suites of genes are differentially regulated.

Formation of a biofilm begins with the attachment of free-floating microorganisms to a surface. These first colonists initially form a weak, reversible adhesion to the surface via van der Waals forces. If the colonists are not immediately separated from the surface, they can anchor themselves more permanently using cell adhesion structures such as pili. Some species are not able to attach to a surface on their own but are able to anchor themselves to the matrix or directly to earlier colonists. It is during this colonization that the cells are able to communicate via quorum sensing using such products as AHL. Once colonization has begun, the biofilm grows through a combination of cell division and recruitment. The final stage of biofilm formation is known as development; this is the stage in which the biofilm is established and may change only in shape and size. The development of a biofilm may allow for an aggregate cell colony (or colonies) to be antibiotic-resistant.

In sum, the five stages of biofilm development are as follows:

1. Initial attachment
2. Irreversible attachment
3. Maturation I
4. Maturation II
5. Dispersion

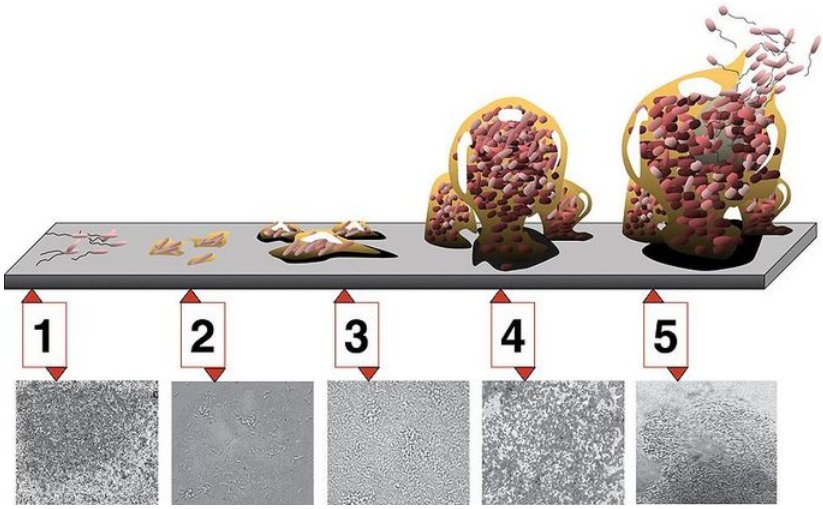

Figure: ***The Five Stages of Biofilm Development****: Stage 1: initial attachment; stage 2: irreversible attachment; stage 3: maturation I; stage 4: maturation II; stage 5: dispersion. Each stage of development in the diagram is paired with a photomicrograph of a developing Pseudomonas aeruginosa biofilm. All photomicrographs are shown at the same scale.*

Dispersal of cells from the biofilm colony is an essential stage of the biofilm life cycle. Dispersal enables biofilms to spread and colonize new surfaces. Enzymes that degrade the biofilm extracellular matrix, such as dispersin B and deoxyribonuclease, may play a role in biofilm dispersal. Biofilm matrix-degrading enzymes may be useful as anti-biofilm agents. Recent evidence has shown that one fatty acid messenger, cis-2-decenoic acid, is capable of inducing dispersion and inhibiting growth of biofilm colonies.

Secreted by Pseudomonas aeruginosa, this compound induces cyclo heteromorphic cells in several species of bacteria and the yeast Candida albicans. Nitric oxide has also been shown to trigger the dispersal of biofilms of several bacteria species at sub-toxic concentrations, so it shows potential for use in the treatment of patients that suffer from chronic infections caused by biofilms.

Bacteria living in a biofilm usually have significantly different properties from free-floating bacteria of the same species, as the dense and protected environment of the film allows them to cooperate and interact in various ways. One benefit of this environment is increased resistance to detergents and antibiotics, as the dense extracellular matrix and the outer layer of cells protect the interior of the community. In some cases antibiotic resistance can be increased a thousandfold. Lateral gene transfer is also greatly facilitated in biofilms and leads to a more stable structure.

However, biofilms are not always less susceptible to antibiotics. For instance, the biofilm form of *Pseudomonas aeruginosa* has no greater resistance to antimicrobials than do stationary-phase planktonic cells, although when the biofilm is compared to logarithmic-phase planktonic cells, the biofilm does show greater resistance to antimicrobials. This resistance to antibiotics in both stationary phase cells and biofilms may be due to the presence of persister cells.

Key Points

- Microbes form a biofilm in response to many factors, including cellular recognition of specific or non-specific attachment sites on a surface, nutritional cues, or exposure of planktonic cells to sub-inhibitory concentrations of antibiotics.
- Formation of a biofilm begins with the attachment of free-floating microorganisms to a surface. These first colonists initially adhere to the surface through weak, reversible adhesion via van der Waals forces.
- If the colonists are not immediately separated from the surface, they can anchor themselves more permanently using cell adhesion structures such as pili.

Key Terms

- **biofilm**: an aggregate of microorganisms in which cells adhere to each other on a surface

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SECTION OVERVIEW

6. 12: Control in Microbial Death

Topic hierarchy

6.12A: Considerations in Microbial Control

6.12B: Rate of Microbial Death

6.12C: Relative Resistance of Microbes

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6.12A: Considerations in Microbial Control

Controlling microbial growth is important in many fields but the degree of acceptable microbial levels can be quite different.

LEARNING OBJECTIVES

Discover considerations in microbial control

Key Takeaways

Key Points

- Controlling microbial growth is important in the medical field, pharmaceutical and biotechnology industries, academic research, and food industry.
- The degree of acceptable microbial presence can differ based on the circumstances. Sterilization as a definition means that all life was terminated, whereas sanitization and disinfection terminates selectively and partially.
- Chemical agents that can eliminate or suppress microbial life are separated in different groups based on their use. The major groups are disinfectants, antiseptics, and antibiotics.
- Antibacterials are divided into two broad groups according to their biological effect on microorganisms: bactericidal agents kill bacteria, and bacteriostatic agents slow down or stall bacterial growth.

Key Terms

- **sterilization**: Any process that eliminates or kills all forms of microbial life present on a surface, solution, or solid compound.
- **microbicides**: Compounds or substances whose purpose is to reduce the infectivity of microbes, such as viruses or bacteria.
- **parenteral**: Administered by some means other than oral intake, particularly intravenously or by injection.

Considerations in Microbial Control

Ever since microbes were shown to cause diseases, people have invented different techniques to control their spread. Controlling microbial growth is important in the medical field, pharmaceutical and biotechnology industries, academic research, and food industry. Each antimicrobial substance or agent achieves a different level of microbial elimination by a certain mechanism.

TYPES OF MICROBIAL CONTROL

Sterilization (or sterilisation) is a term referring to any process that eliminates (removes) or kills all forms of microbial life, including transmissible agents (such as fungi, bacteria, viruses, and spore forms) present on a surface, contained in a fluid, in medication, or in a compound. Sterilization can be achieved by applying the proper combinations of heat, chemicals, irradiation, high pressure, and filtration.

Chemical agents that can eliminate or suppress microbial life are separated in different groups based on their use.

Disinfectants are substances that are applied to non-living objects to destroy microorganisms that are living on them. Disinfection does not necessarily kill all microorganisms, especially resistant bacterial spores, so it is less effective than sterilisation. Disinfectants are different from other antimicrobial agents such as antibiotics, which destroy microorganisms within the body. Disinfectants are also different from biocides, as these are intended to destroy all forms of life, not just microorganisms. Disinfectants work by destroying the cell wall of microbes or interfering with their metabolism.

Antiseptics are antimicrobial substances that are applied to living tissue or skin to reduce the possibility of infection, sepsis, or putrefaction. Antiseptics are generally distinguished from antibiotics by the latter’s ability to be transported through the lymphatic system to destroy bacteria within the body, and from disinfectants, which destroy microorganisms found on non-living objects.

The term antibiotic was first used in 1942 by Selman Waksman and his collaborators in journal articles to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This definition excluded substances that kill bacteria, but are not produced by microorganisms (such as gastric juices and hydrogen peroxide). It also excluded synthetic antibacterial compounds such as the sulfonamides. With advances in medicinal chemistry, most of today’s antibacterials chemically are semisynthetic modifications of various natural compounds.

Many antibacterial compounds are classified on the basis of chemical or biosynthetic origin into natural, semisynthetic, and synthetic. Another classification system is based on biological activity. In this classification, antibacterials are divided into two

broad groups according to their biological effect on microorganisms: bactericidal agents kill bacteria, andbacteriostatic agents slow down or stall bacterial growth.

Microbicides which destroy virus particles are called viricides or antivirals.

LEVEL OF MICROBIAL PRESENCE

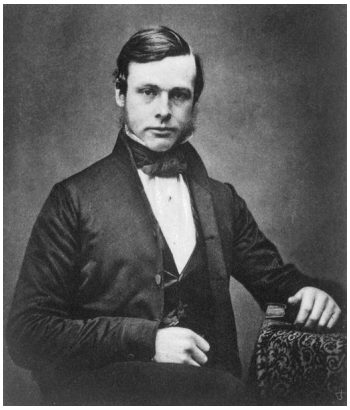

Figure: **Joseph Lister**: Joseph Lister was one of the first to use aseptic techniques during surgeries.

The degree of acceptable microbial presence can differ based on the circumstances. Sterilization as a definition means that all life was terminated, whereas sanitization and disinfection terminates selectively and partially. Both sanitization and disinfection reduce the number of targeted pathogenic organisms to what are considered “acceptable” levels – levels that a reasonably healthy, intact body can deal with.

In general, surgical instruments and medications that enter an already aseptic part of the body (such as the bloodstream, or penetrate the skin) must be sterilized to a high sterility assurance level (SAL). Examples of such instruments include scalpels, hypodermic needles, and artificial pacemakers. For example, medical device manufacturers design their sterilization processes for an extremely low SAL. Their “one in a million” devices should be nonsterile.

This is also essential in the manufacture of parenteral pharmaceuticals. Preparation of injectable medications and intravenous solutions for fluid replacement therapy requires not only a high sterility assurance level, but also well-designed containers to prevent entry of adventitious agents after the initial product sterilization.

Food preservation is another field where the presence of microorganisms is taken under consideration. The process usually involves preventing the growth of bacteria, fungi (such as yeasts), and other microorganisms (although some methods work by introducing benign bacteria or fungi to the food).

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6.12B: Rate of Microbial Death

Learning Objectives

- Describe microbial death rates

The rate of microbial death can be determined. It is important in order to develop standard protocols for disinfection which will facilitate the sterilization routine in many industries. The goal is to find out what is the minimum time needed to achieve acceptable level of sterilization for a specific purpose. The killing agent can be different (e.g., heat, chemical with certain concentration) depending on the specific application.

When the killing factor is heat, the phrase thermal death can be used. Thermal death time is a concept used to determine how long it takes to kill a specific bacteria at a specific temperature. It was originally developed for food canning and has found applications in cosmetics, and in producing salmonella-free feeds for animals (e.g. poultry, and pharmaceuticals).

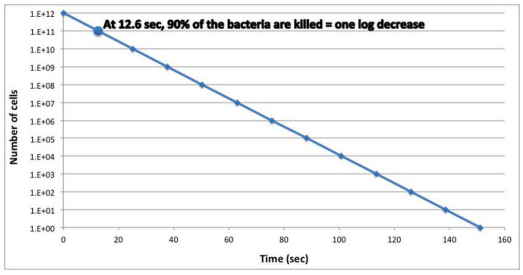

Figure: **Killing curve of C. botulinum**: This curve presents the DR value (12.6 seconds) and the 12-D reduction (151 seconds) for C. botulinum. The killing agent is heat at 121ºC.

In the food industry, it is important to reduce the amount of microbes in products to ensure proper food safety. This is usually done by thermal processing and finding ways to reduce the number of bacteria in the product. Time-temperature measurements of bacterial reduction is determined by a D-value, meaning how long it would take to reduce the bacterial population by 90% or one $\log_{10}$ at a given temperature. This D-value reference (D_R) point is 121°C.

Z or z-value is used to determine the time values with different D-values at different temperatures with its equation shown below:

$$z = T_2 - T_1 \log D_1 - \log D_2 z = T_2 - T_1 \log D_1 - \log D_2 \quad (6.12B.1)$$

where T is temperature in °C. Such death curves can be empirically established for all bactericidal agents. This D-value is affected by pH of the product where low pH has faster D values on various foods. The D-value at an unknown temperature can be calculated knowing the D-value at a given temperature provided the Z-value is known. The target of reduction in canning is the 12-D reduction of *Clostridium botulinum*, which means that processing time will reduce the amount of this bacteria by 10^{12} bacteria per gram or milliliter. The D_R for *C. botulinum* is 12.6 seconds. A 12-D reduction will take 151 seconds.

Key Points

- When researching microbial death rate, the goal is usually to find out the minimum time needed to achieve acceptable level of sterilization for a specific purpose.
- Bacterial reduction is determined by a D-value, meaning how long it would take to reduce the bacterial population by 90% or one log10 at a given state of the killing agent.
- Microbial death curves have been developed for many agents and are used in numerous industries.

Key Terms

- **D-value**: The time needed to reduce the bacterial population by 90% or one log10 at a given temperature.
- **12-D reduction**: The time needed to reduce the amount of bacteria by 1012 bacteria per gram or milliliter.

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6.12C: Relative Resistance of Microbes

Different microbial structures and types of microbial cells have different level of resistance to antimicrobial agents.

LEARNING OBJECTIVES

Contrast the relative resistance of microbes

Key Takeaways

Key Points

- Endospores are considered the most resistant structure of microbes. They are resistant to most agents that would normally kill the vegetative cells they formed from.
- Mycobacterial infections are notoriously difficult to treat. Protozoa cysts are quite hard to eliminate too. Gram negative species have high levels of natural antibiotic resistance. Staphylococcus aureus is one of the major resistant human pathogens.
- Fungal cells as well as spores are more susceptible to treatments. Vegetative bacterial and yeasts cells are some of the easiest to eliminate with different treatment methods. Viruses, especially enveloped ones, are relatively easy to treat successfully with chemicals due to the presence of lipids.

Key Terms

- **horizontal gene transfer**: The transfer of genetic material from one organism to another one that is not its offspring; especially common among bacteria.
- **endospores**: An endospore is a dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.

Different microbial structures and types of microbial cells have different level of resistance to antimicrobial agents used to eliminate them.

Endospores are considered the most resistant structure of microbes. They are resistant to most agents that would normally kill the vegetative cells from which they formed. Nearly all household cleaning products, alcohols, quaternary ammonium compounds and detergents have little effect. However, alkylating agents (e.g. ethylene oxide), and 10% bleach are effective against endospores. Endospores are able to survive boiling at 100°C for hours. Prolonged exposure to ionizing radiation, such as x-rays and gamma rays, will also kill most endospores.

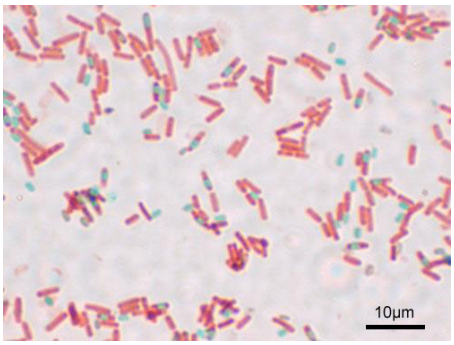

Figure: **Bacillus subtilis stained with the Schaeffer-Fulton stain.**: A stained preparation of Bacillus subtilis showing endospores as green and the vegetative cell as red.

Certain bacterial species are more resistant to treatment than others. Mycobacterial infections are notoriously difficult to treat. The organisms are hardy due to their cell wall, which is neither truly Gram negative nor positive. In addition, they are naturally resistant to a number of antibiotics that disrupt cell-wall biosynthesis, such as penicillin. Due to their unique cell wall, they can survive long exposure to acids, alkalis, detergents, oxidative bursts, lysis by complement, and many antibiotics. Most mycobacteria are susceptible to the antibiotics clarithromycin and rifamycin, but antibiotic-resistant strains have emerged.

Protozoa cysts are quite hard to eliminate too. As cysts, protozoa can survive harsh conditions, such as exposure to extreme temperatures or harmful chemicals, or long periods without access to nutrients, water, or oxygen for a period of time. Being a cyst enables parasitic species to survive outside of a host, and allows their transmission from one host to another. Protozoa cells are also hardy to eliminate.

Gram-negative bacteria have high natural resistance to some antibiotics. Examples include *Pseudomonas* spp. which are naturally resistant to penicillin and the majority of related beta-lactam antibiotics. This ability to thrive in harsh conditions is a result of their hardy cell wall that contains porins. Their resistance to most antibiotics is attributed to efflux pumps, which pump out some antibiotics before the antibiotics are able to act.

Staphylococcus aureus is one of the major resistant pathogens. Found on the mucous membranes and the human skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was one of the earlier bacteria in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first detected in Britain in 1961, and is now “quite common” in hospitals. A recent study demonstrated that the extent of horizontal gene transfer among *Staphylococcus* is much greater than previously expected—and encompasses genes with functions beyond antibiotic resistance and virulence, and beyond genes residing within the mobile genetic elements.

Fungal cells as well as spores are more susceptible to treatments. Vegetative bacterial and yeasts cells are some of the easiest to eliminate with numerous agents and methods. Viruses, especially enveloped ones, are relatively easy to treat successfully with chemicals due to the presence of lipids.

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SECTION OVERVIEW

6. 13: Mechanisms of Microbial Control

Topic hierarchy

6.13A: Alteration of Membrane Permeability

6.13B: Damage to Proteins and Nucleic Acids

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6.13A: Alteration of Membrane Permeability

Learning Objectives

- Illustrate the alteration of membrane permeability on microbial growth

As a phospholipid bilayer, the lipid portion of the outer membrane is impermeable to charged molecules. However, channels called porins are present in the outer membrane that allow for passive transport, across the outer membrane, of many ions, sugars, and amino acids. These molecules are present in the periplasm, the region between the cytoplasmic and outer membranes. The periplasm contains the peptidoglycan layer and also many proteins responsible for substrate binding or hydrolysis and the reception of extracellular signals. The periplasm is thought to exist as a gel-like state rather than a liquid due to the high concentration of proteins and peptidoglycan found within it. Because of its location between the cytoplasmic and outer membranes, signals received and substrates bound are available to be transported across the cytoplasmic membrane using transport and signalling proteins that are embedded there.

Antimicrobial Drugs

Examples of antimicrobial drugs that can target the microbial cell membrane to alter its functionality include polymyxin and gramicidin.

After binding to lipopolysaccharide (LPS) in the outer membrane of gram-negative bacteria, polymyxins disrupt both the outer and inner membranes. The hydrophobic tail is important in causing membrane damage, suggesting a detergent-like mode of action. Removal of the hydrophobic tail of polymyxin B yields polymyxin nonapeptide, which still binds to LPS but no longer kills the bacterial cell. However, it still increases the permeability of the bacterial cell wall to other antibiotics, indicating that it causes some degree of membrane disorganization. Gram-negative bacteria can develop resistance to polymyxins through various modifications of the LPS structure that inhibit the binding of polymyxins to LPS.

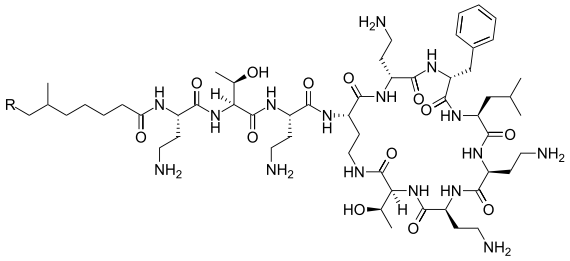

Figure: **Polymyxin B**: Polymyxin B has a hydrophobic tail that causes membrane damage.

Gramicidin is a heterogeneous mixture of six antibiotic compounds, gramicidins A, B, and C, making up 80%, 6%, and 14% respectively, all of which are obtained from the soil bacterial species *Bacillus brevis* and called collectively gramicidin D. Gramicidin D is made of linear pentadecapeptides, chains made of 15 amino acids. This is in contrast to gramicidin S, which is a cyclic peptide chain.

Gramicidin is active against gram-positive bacteria, except for gram-positive bacilli, and against selective gram-negative organisms, such as *Neisseria* bacteria. The therapeutic use of gramicidin is limited to topical application, as it induces hemolysis in lower concentrations and then bacteria cell death, so cannot be administered internally. Since the exterior epidermis is composed of dead cells, applying it to the skin's surface does not cause harm.

Gramicidin is used primarily as a topical antibiotic and is one of the three constituents of the consumer antibiotic polysporin ophthalmic solution. Gramicidin's bactericidal activity is a result of increasing the permeability of the bacterial cell membrane, allowing inorganic monovalent cations (e.g. Na^+) to travel through unrestricted and thereby destroy the ion gradient between the cytoplasm and the extracellular environment.

Gramicidin D functioning as a channel was demonstrated by Hladky and Haydon, who investigated the unit conductance channel. In general, gramicidin channels are ideally selective for monovalent cations and the single-channel conductances for the alkali cations are ranked in the same order as the aqueous mobility of these ions. Divalent cations like $Ca2^+$ block the channel by binding near its mouth so that it is essentially impermeable to divalent cations, and also excludes anions. Cl^- in particular is excluded from the channel because its hydration shell is thermodynamically stronger than the shells of most monovalent cations. The channel is

permeable to most monovalent cations, which move through the channel in single file. The channel is filled with about six water molecules, almost all of which must be displaced when an ion is transported. Thus, ions moving through the gramicidin pore carry a single file of water molecules. The flow of ion molecules and water molecules is known as flux coupling. In the presence of a second type of permeable ion, the two ions couple their flux as well. Like valinomycin and nonactin, the gramicidin channel is selective for potassium over sodium but only slightly so. It has a permeability ratio of 2.9. Though it is impermeable to anions, there are conditions under which some anion permeation may be observed. Its ability to bind and transport cations is due to the presence of cation-binding sites, one strong and the other weak, in the channel.

Key Points

- Antimicrobial drugs can target the microbial cell membrane to alter its functionality. Examples include: polymyxin and gramicidin.
- After binding to lipopolysaccharide in the outer membrane of gram-negative bacteria, polymyxins disrupt both the outer and inner membranes.
- Gramicidin's bactericidal activity is a result of increasing the permeability of the bacterial cell membrane, allowing inorganic monovalent cations (e.g. Na+) to travel through unrestricted and thereby destroy the ion gradient between the cytoplasm and the extracellular environment.

Key Terms

- **membrane**: A flexible enclosing or separating tissue forming a plane or film and separating two environments (usually in a plant or animal).
- **antimicrobial**: An antimicrobial substance kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic).
- **permeable**: Of or relating to substance, substrate, membrane or material that absorbs or allows the passage of fluids.

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6.13B: Damage to Proteins and Nucleic Acids

Learning Objectives

- Explain how microbes are controlled through DNA and protein damage

A bacteriostatic agent or bacteriostat, abbreviated Bstatic, is a biological or chemical agent that stops bacteria from reproducing, while not necessarily harming them. Depending on their application, bacteriostatic antibiotics, disinfectants, antiseptics, and preservatives can be distinguished. Upon removal of the bacteriostat, the bacteria usually start to grow again. This is in contrast to bactericides, which kill bacteria.

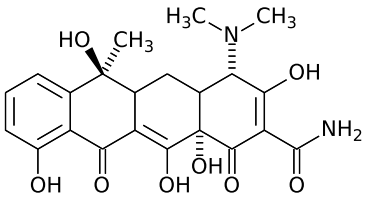

Figure: ***Tetracycline****: Chemical structure of Tetracycline ((4S,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide).*

Bacteriostats are often used in plastics to prevent growth of bacteria on surfaces. Bacteriostats commonly used in laboratory work include sodium azide (which is acutely toxic) and thiomersal (which is a mutagen in mammalian cells).

Bacteriostatic antibiotics limit the growth of bacteria by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism. They must work together with the immune system to remove the microorganisms from the body. However, there is not always a precise distinction between them and bactericidal antibiotics. High concentrations of some bacteriostatic agents are also bactericidal, whereas low concentrations of some bacteriocidal agents are bacteriostatic.

This group of drugs include: Tetracyclines, sulfonamides, Spectinomycin, Trimethoprim, Chloramphenicol, Macrolides, and Lincosamides.

Tetracycline is a broad-spectrum polyketide antibiotic produced by the *Streptomyces* genus of Actinobacteria, indicated for use against many bacterial infections. It is a protein synthesis inhibitor. It is commonly used to treat acne today, and, more recently, rosacea, and is historically important in reducing the number of deaths from cholera. Tetracycline is marketed under the brand names Sumycin, Tetracyn, and Panmycin, among others. Actisite is a thread-like fiber formulation used in dental applications. It is also used to produce several semisynthetic derivatives, which together are known as the tetracycline antibiotics. The term “tetracycline” is also used to denote the four-ring system of this compound. “Tetracyclines” are related substances that contain the same four-ring system.

Key Points

- Bacteriostatic antibiotics limit the growth of bacteria by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism.
- Upon removal of the bacteriostat, the bacteria usually start to grow again.
- Bacteriostatic antibiotics must work together with the immune system to remove the microorganisms from the body.

Key Terms

- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.
- **bacteria**: A type, species, or strain of bacterium.
- **replication**: Process by which an object, person, place or idea may be copied mimicked or reproduced.

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SECTION OVERVIEW

6. 14: Physical Antimicrobial Control

Topic hierarchy

6.14A: Heat

6.14B: Radiation

6.14C: Low Temperatures

6.14D: High Pressure

6.14E: Desiccation

6.14F: Osmotic Pressure

6.14G: Filtration

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6.14A: Heat

Learning Objectives

- Evaluate heat as an agent of microbrial control

Applying heat to bacterial media and utensils in research and the medical field as well as to sterilize food is one of the most common methods for control of bacterial growth. To achieve sterilization, different techniques and tools are used.

Moist Heat Sterilization

Moist heat causes destruction of micro- organisms by denaturation of macromolecules, primarily proteins. Autoclaving (pressure cooking) is a very common method for moist sterilization. It is effective in killing fungi, bacteria, spores, and viruses but does not necessarily eliminate prions. When sterilizing in this way, samples are placed into a steam chamber. The chamber is closed and heated so that steam forces air out of the vents or exhausts. Pressure is then applied so that the interior temperature reaches 121°C. This temperature is maintained for between 15 and 30 minutes. This elevated temperature and pressure is sufficient to sterilize samples of any commonly encountered microbes or spores. The chamber is then allowed to cool slowly or by passive heat dissipation.

Pressure sterilization is the prevailing method used for medical sterilization of heat-resistant tools. It is also used for sterilization of materials for microbiology and other fields calling for aseptic technique. To facilitate efficient sterilization by steam and pressure, there are several methods of verification and indication used; these include color-changing indicator tapes and biological indicators. For any method of moist heat sterilization, it is common to use biological indicators as a means of validation and confirmation. When using biological indicators, samples containing spores of heat-resistant microbes such as *Geobacillus stearothermophilis* are sterilized alongside a standard load, and are then incubated in sterile media (often contained within the sample in a glass ampoule to be broken after sterilization). A color change in the media (indicating acid production by bacteria; requires the medium to be formulated for this purpose) or the appearance of turbidity (cloudiness indicating light scattering by bacterial cells) indicates that sterilization was not achieved and the sterilization cycle may need revision or improvement. Other moist methods are boiling samples for certain period of time and Tyndallisation. Boiling is not efficient in eliminating spores. Tyndallisation inactivates spores as well, but is a more lengthy process.



Figure: ***Autoclave**: Large autoclave used for moist sterilization of media and equipment*

Dry Heat Sterilization

Dry heat destroys microorganisms by causing coagulation of proteins. The dry heat sterilization process is accomplished by conduction; that is where heat is absorbed by the exterior surface of an item and then passed inward to the next layer. Eventually, the entire item reaches the proper temperature needed to achieve sterilization. The time and temperature for dry heat sterilization is 160°C for 2 hours or 170°C for 1 hour. Instruments should be dry before sterilization since water will interfere with the process. Other heat sterilization methods include flaming and incineration. Flaming is commonly used to sterilize small equipment used to manipulate bacteria aseptically. Leaving transfer loops in the flame of a Bunsen burner or alcohol lamp until it glows red ensures that any infectious agent gets inactivated. This is commonly used for small metal or glass objects, but not for large objects (see Incineration below). However, during the initial heating infectious material may be “sprayed” from the wire surface before it is killed, contaminating nearby surfaces and objects. Therefore, special heaters have been developed that surround the inoculating

loop with a heated cage, ensuring that such sprayed material does not further contaminate the area. Another problem is that gas flames may leave residues on the object, e.g. carbon, if the object is not heated enough. A variation on flaming is to dip the object in 70% ethanol (or a higher concentration) and merely touch the object briefly to the Bunsen burner flame, but not hold it in the gas flame. The ethanol will ignite and burn off in a few seconds. 70% ethanol kills many, but not all, bacteria and viruses. It has the advantage that it leaves less residue than a gas flame. This method works well for the glass “hockey stick”-shaped bacteria spreaders. Incineration will also burn any organism to ash. It is used to sanitize medical and other bio hazardous waste before it is discarded with non-hazardous waste.

Key Points

- Different methods are used to achieve sterilization. One of the most common is applying moist heat which includes autoclaving (pressure cooking), boiling, and Tyndallisation.
- Dry heat sterilization is accomplished by conduction and is used widely for instruments.
- Other heat methods include flaming and incineration. Flaming is commonly used to sterilize small equipment used to manipulate bacteria aseptically.

Key Terms

- **sterilization**: Any process that eliminates or kills all forms of microbial life present on a surface, solution, or solid compound.
- **Tyndallisation**: Tyndallisation is the process of three successive steam treatments to achieve sterilization over the course of three days. This works by killing vegetative cells, allowing germination of surviving spores, and killing the resulting vegetative cells before they have time to form further spores.

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6.14B: Radiation

Learning Objectives

- Compare non-ionizing and ionizing radiation in terms of microbe inhibition

Both non-ionizing and ionizing radiation methods are applied for sterilization.

Non-ionizing Radiation Sterilization

Ultraviolet light irradiation (UV, from a germicidal lamp) is useful only for sterilization of surfaces and some transparent objects. Many objects that are transparent to visible light such as glass, absorb UV. UV irradiation is routinely used to sterilize the interiors of biological safety cabinets between uses, but is ineffective in shaded areas. The drawback of UV radiation is that it damages some plastics, such as polystyrene foam, if they are exposed for prolonged periods of time.

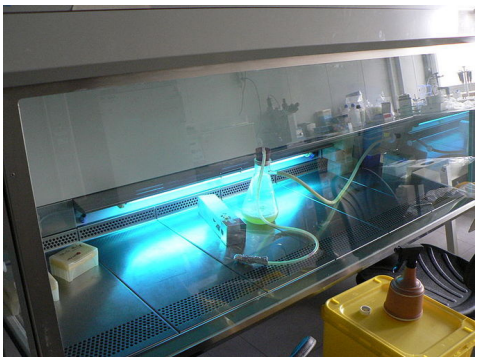

Figure: ***UV light used in the laboratory****: UV light is commonly used to irradiate and sterilize laminar flow cabinets between uses.*

Ionizing Radiation Sterilization

Ionizing radiation could be a lethal health hazard if used inappropriately. The proper use of these methods is regulated and monitored by world and national safety organizations. Any incidents that have occurred in the past are documented and thoroughly analyzed to determine root cause and improvement potential.

- **Gamma rays**: Gamma rays are very penetrating and are commonly used for sterilization of disposable medical equipment, such as syringes, needles, cannulas and IV sets, and food. The gamma radiation is emitted from a radioisotope (usually cobalt-60 or cesium-137). Cesium-137 is used in small hospital units to treat blood before transfusion to prevent **Graft-versus-host disease**. Use of a radioisotope requires shielding to ensure the safety of the operators while in use and in storage as these radioisotopes continuously emits gamma rays (cannot be turned off). An incident in Decatur, Georgia where water soluble cesium-137 leaked into the source storage pool requiring NRC intervention has led to near elimination of this radioisotope; it has been replaced by the more costly, non-water soluble cobalt-60. Sterilization by irradiation with gamma rays may, in some cases affect material properties.
- **Electron beams:** Electron beam processing is also commonly used for sterilization. Electron beams use an on-off technology and provide a much higher dosing rate than gamma or x-rays. Due to the higher dose rate, less exposure time is needed and thereby any potential degradation to polymers is reduced. A limitation is that electron beams are less penetrating than either gamma or x-rays. Facilities rely on substantial concrete shields to protect workers and the environment from radiation exposure.
- **X-rays**: High-energy X-rays are a form of ionizing energy allowing to irradiate large packages and pallet loads of medical devices. X-ray sterilization is an electricity based process that does not require chemical or radioactive material. High energy and high power X-rays are generated by an X-ray machine that can be turned off when not in use, and therefore does not require any shielding when in storage. Irradiation with X-rays or gamma rays does not make materials radioactive.
- **Subatomic particles:** Subatomic particles may be more or less penetrating, and may be generated by a radioisotope or a device, depending on the type of particle. Irradiation with particles may make materials radioactive, depending on the type of particles, their energy, and the type of target material: neutrons and very high-energy particles can make materials radioactive but have good penetration, whereas lower energy particles (other than neutrons) cannot make materials radioactive, but have poorer penetration.

Irradiation is used by the United States Postal Service to sterilize mail in the Washington, DC area. Some foods (e.g. spices, ground meats) are irradiated for sterilization.

Key Points

- Ultraviolet light irradiation is a non-ionizing method useful only for sterilization of surfaces and some transparent objects.
- Common methods of ionizing radiation are gamma rays, electron beams, X-rays, and subatomic particles.
- However, ionizing radiation could be a lethal health hazard if used inappropriately. The proper use of these methods is regulated and monitored by world and national safety organizations.

Key Terms

- **Graft-versus-host disease**: A complication after tissue or organ transplant or blood transfusion if the blood was not irradiated. White blood cells of the transplanted tissue or organ (the graft) attack cells in the recipients body (the host).
- **NRC**: Nuclear Regulatory Commission

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6.14C: Low Temperatures

Learning Objectives

- Identify how low temperatures are used for microbial control

Temperature is an important factor for microbial growth. Each species has its own optimal growth temperature at which it flourishes. Human microbial pathogens usually thrive at body temperature, 37ºC. Low temperatures usually inhibit or stop microbial growth and proliferation but often do not kill bacteria. Refrigeration (4ºC) and freezing (-20ºC or less) are commonly used in the food, pharmaceuticals and biotechnology industry.

Refrigeration preserves food by slowing down the growth and reproduction of microorganisms and the action of enzymes which cause food to rot. The introduction of commercial and domestic refrigerators drastically improved the diets of many in the 1930s by allowing foods such as fresh fruit, salads and dairy products to be stored safely for longer periods, particularly during warm weather. It also facilitated transportation of fresh food on long distances.



Figure: **The Dunedin**: This ship executed the first completely successful refrigerated shipment of food.

Refrigeration is also used to facilitate the preservation of liquid medicines or other substances used for research where microbial growth is undesirable, often combined with added preservatives. Fridge temperatures inhibit the proliferation of bacteria better than molds and fungi.

For longer periods of preservation, freezing temperatures are preferred to refrigeration. Since early times, farmers, fishermen, and trappers have preserved their game and produce in unheated buildings during the winter season. Freezing food slows down decomposition by turning residual moisture into ice, inhibiting the growth of most bacterial species.

Freezing temperatures curb the spoiling effect of microorganisms in food, but can also preserve some pathogens unharmed for long periods of time. While it kills some microorganisms by physical trauma, others are sublethally injured by freezing, and may recover to become infectious.

Frozen products do not require any added preservatives because microorganisms do not grow when the temperature of the food is below -9.5°C, which is sufficient in itself to prevent food spoilage. Long-term preservation of food may call for food storage at even lower temperatures.

Key Points

- Refrigeration (4ºC) and freezing (-20ºC or less) are commonly used in food, pharmaceutical and biotechnology industries.
- Refrigeration preserves food by slowing down the growth and reproduction of microorganisms as well as the action of enzymes which cause food to rot.
- Freezing food slows down decomposition by turning residual moisture into ice, inhibiting the growth of most bacterial species. Freezing kills some microorganisms by physical trauma, while sublethally injuring others which may recover to become infectious.

Key Terms

- **proliferation**: The process by which an organism produces others of its kind; breeding, propagation, procreation, reproduction.

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6.14D: High Pressure

Under very high hydrostatic pressure(HHP) of up to 700 MPa, water inactivates pathogens such as *E. coli and Salmonella*.

LEARNING OBJECTIVES

Explain high pressure as a antimicrobial control

Key Takeaways

Key Points

- High pressure processing (HPP), pascalization or bridgmanization, is a method of preserving and sterilizing food, in which a product is processed under very high pressure, leading to the inactivation of certain microorganisms and enzymes in the food.
- The frist reports showed that bacterial spores were not always inactivated by pressure, while vegetative bacteria were usually killed. Later it was discovered that using moderate pressures was more effective in eliminating spores than using higher pressures.
- Experiments were also performed with anthrax, typhoid, and tuberculosis, which was a potential health risk for the researchers.

Key Terms

- **bridgmanization**: Pascalization is also known as bridgmanization, named for physicist Percy Williams Bridgman.

Under very high hydrostatic pressure of up to 700 MPa (100,000 psi), water inactivates pathogens such as *Listeria*, *E. coli and Salmonella*.

High pressure processing (HPP), pascalization or bridgmanization, is a method of preserving and sterilizing food, in which a product is processed under very high pressure, leading to the inactivation of certain microorganisms and enzymes in the food. The technique was named after Blaise Pascal, whose work included detailing the effects of pressure on fluids. Pascalization is preferred over heat treatment in the food industry as it eliminates changes in the quality of foods due to thermal degradation, resulting in fresher taste, texture, appearance and nutrition. Processing conveniently takes place at ambient or refrigeration temperatures.

Experiments into the effects of pressure on microorganisms were first recorded in the late nineteenth century. The frist reports showed that bacterial spores were not always inactivated by pressure, while vegetative bacteria were usually killed. Around 1970, researchers renewed their efforts in studying bacterial spores after it was discovered that using moderate pressures was more effective than using higher pressures. These spores, which caused a lack of preservation in the earlier experiments, were inactivated faster by moderate pressure, but in a manner different from what occurred with vegetative microbes. When subjected to moderate pressures, bacterial spores germinate, and the resulting spores are easily killed using pressure, heat, or ionizing radiation.

Research into the effects of high pressures on microorganisms was largely focused on deep-sea organisms until the 1980s, when advancements in ceramic processing were made. This resulted in the production of machinery that allowed for processing foods at high pressures at a large scale, and generated some interest in the technique, especially in Japan. Although commercial products preserved by pascalization first emerged in 1990, the technology behind pascalization is still being perfected for widespread use.



Figure: **Japanese miso soup**: Miso soup is sterilized with high pressure.

In pascalization, food products are sealed and placed into a steel compartment containing a liquid, often water, and pumps are used to create pressure. The pumps may apply pressure constantly or intermittently. During pascalization, more than 50,000 pounds per square inch (340 MPa) may be applied for around fifteen minutes, leading to the inactivation of yeast, mold, and bacteria. In the

process, the food's proteins are denatured, hydrogen bonds are fortified, and noncovalent bonds in the food are disrupted, while the product's main structure remains intact. Because pascalization is not heat-based, covalent bonds are not affected, causing no change in the food's taste.

Experiments were also performed with anthrax, typhoid, and tuberculosis, which was a potential health risk for the researchers. Indeed, before the process was improved, one employee of the Experimental Station became ill with typhoid fever.

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6.14E: Desiccation

Desiccation is the state of extreme dryness, or the process of extreme drying and can be used to control microbial growth.

LEARNING OBJECTIVES

Show how desiccation inhibits microbes

Key Takeaways

Key Points

- Microorganisms cannot grow and divide when desiccated, but can survive for certain periods of time, depending on their features. After the addition of water, the bacteria will start growing again, so desiccation does not provide complete sterilization.
- Pharmaceutical companies often use freeze-drying as a desiccation tool to increase the shelf life of products, such as vaccines and other injectables. Drying is also a method for food preservation.
- Freeze-drying is performed using special equipment.

Key Terms

- **desiccation**: the state of drying
- **freeze-drying**: Freeze-drying, also known as lyophilisation, lyophilization, or cryodesiccation, is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport.

Desiccation is the state of extreme dryness, or the process of extreme drying. In biology and ecology, desiccation refers to the drying out of a living organism. Microorganisms cannot grow and divide when desiccated, but can survive for certain periods of time, depending on their features. After the addition of water, the bacteria will start growing again, so desiccation does not provide complete sterilization.



Figure: **SMART Freeze Dryer**: New freeze dryer which is equipped with systems for immediate feedback on the properties of the dried product, eliminating the lengthy trial-and-error approach.

Some bacteria, such as *Deinococcus radiodurans* and *Mycobacterium* , are extremely resistant to damage from prolonged desiccation while others, such as *Neisseria gonorrhoeae*, can survive only short periods of desiccation.

Pharmaceutical companies often use freeze-drying as a desiccation tool to increase the shelf life of products, such as vaccines and other injectables. By removing the water from the material and sealing the material in a vial, the material can be easily stored, shipped, and later reconstituted to its original form. Preservation is possible because the greatly reduced water content inhibits the

action of microorganisms and enzymes that would normally spoil or degrade the substance. Another example from the pharmaceutical industry is the use of freeze-drying to produce tablets or wafers.

Drying is also a method for food preservation that works by removing water from the food, which inhibits the growth of microorganisms. Open air drying using sun and wind has been practiced since ancient times to preserve food. A solar or electric food dehydrator can greatly speed the drying process and ensure more consistent results. Water is usually removed by evaporation (air drying, sun drying, smoking, or wind drying) but, in the case of freeze-drying, food is first frozen and then the water is removed by sublimation. Bacteria, yeasts, and molds need the water in the food to grow, and drying effectively prevents them from surviving in food.

Freeze-drying is performed using special equipment. Two components are common to all types of freeze-dryers: a vacuum pump to reduce the ambient gas pressure in a vessel containing the substance to be dried, and a condenser to remove the moisture by condensation on a surface cooled to −40º to −80ºC.

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6.14F: Osmotic Pressure

Osmotic pressure is the pressure which must be applied to a solution to prevent the inward flow of water across a semipermeable membrane.

LEARNING OBJECTIVES

Interpret osmotic pressure as a means of microbial control

Key Takeaways

Key Points

- Osmotic pressure is of vital importance in biology as the cell's membrane is selective toward many of the solutes found in living organisms.
- When a cell is placed in a hypertonic solution, water actually flows out of the cell into the surrounding solution thereby causing the cells to shrink and lose its turgidity. Hypertonic solutions are used for antimicrobial control.
- Salt and sugar are used to create hypertonic environment for microorganisms and are commonly used as food preservatives.

Key Terms

- **turgidity**: Turgidity (turgor pressure) pushes the plasma membrane against the cell wall of plant, bacteria, and fungi cells as well as those protiat cells which have cell walls.

Osmotic pressure is the pressure which needs to be applied to a solution to prevent the inward flow of water across a semipermeable membrane. It is also defined as the minimum pressure needed to nullify osmosis.The phenomenon of osmotic pressure arises from the tendency of a pure solvent to move through a semi-permeable membrane and into a solution containing a solute to which the membrane is impermeable. This process is of vital importance in biology as the cell's membrane is selective toward many of the solutes found in living organisms.



Figure: **Salami**: The original meaning of the word is: all kind of salted (meats).

Osmosis causes water to flow from an area of low solute concentration to an area of high solute concentration until the two areas have an equal ratio of solute to water. Normally, the solute diffuses toward equilibrium as well; however, all cells are surrounded by a lipid bilayer cell membrane which permits the flow of water in and out of the cell but restricts the flow of solute under many circumstances. As a result, when a cell is placed in a hypotonic solution, water rushes into the membrane, increasing its volume. Eventually, the cell's membrane is enlarged such that it pushes against the cell's rigid wall. In an isotonic solution, water flows into the cell at the same rate it flows out. When a cell is placed in a hypertonic solution, water actually flows out of the cell into the surrounding solution causing the cells to shrink and lose its turgidity. Two of the most common substances used to create hypertonic environment for microorganisms and prevent them from growing are salt and sugar. They are widely applied in food preservation.

Table salt (sodium chloride) is the primary ingredient used in meat curing. Removal of water and addition of salt to meat creates a solute-rich environment where osmotic pressure draws water out of microorganisms, thereby retarding their growth. Doing this requires a concentration of salt of nearly 20%.

Sugar is used to preserve fruits, either in syrup with fruit such as apples, pears, peaches, apricots, plums or in crystallized form where the preserved material is cooked in sugar to the point of crystallisation and the resultant product is then stored dry. The purpose of sugaring is to create an environment hostile to microbial life and prevent food spoilage. From time to time, sugaring has also been used for non-food preservation. For example, honey was used as part of the mummification process in some ancient Egyptian rites. However, the growth of molds and fungi is not suppressed as efficiently as the growth of bacteria.

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6.14G: Filtration

Fluids that would be damaged by heat, irradiation, or chemical sterilization can be sterilized by microfiltration using membrane filters.

LEARNING OBJECTIVES

Demonstrate microbial control using filtration

Key Takeaways

Key Points

- A typical microfiltration membrane pore size range is 0.1-10 µm, with the most commonly used being 0.2 µm and 0.45 µm, which is sufficient to eliminate bacteria and fungi.
- Quite often, when biological samples are processed, viruses must be removed or inactivated. Nanofilters with smaller pore sizes of 20-50 nm (nanofiltration) are used.
- Filtration is commonly used for heat labile pharmaceuticals and protein solutions in processing medicines. It is also increasingly used in the treatment of drinking water.

Key Terms

- **ester**: An ester is a chemical compound consisting of a carbonyl group adjacent to an ether linkage.
- **polyethersulfone**: Thermoplastic polymers that have low protein retention. They contain the subunit aryl-SO2-aryl, the defining feature of which is the sulfone group.

Fluids that would be damaged by heat (such as fluids containing proteins like large molecule drug products, but also wine and beer), irradiation, or chemical sterilization can only be sterilized by microfiltration using membrane filters. This method is commonly used for heat labile pharmaceuticals and for protein solutions in processing medicines.

The typical microfiltration membrane pore size range is 0.1-10 µm, with the most commonly used being 0.2 µm; and 0.45 µm is sufficient to eliminate bacteria and fungi.



Figure: **Syringe Filter**: A syringe filter with a pore size of 0.22 micrometers, small enough to capture and retain bacterial and fungal cells.

Microfiltration is increasingly used in drinking water treatment. It effectively removes major pathogens and contaminants such as *Giardia lamblia* cysts, *Cryptosporidium* oocysts, and large bacteria. For this application, the filter has to be rated for 0.2 µm or smaller pore size.

Quite often when biological samples are processed, viruses must be removed or inactivated. Nanofilters with smaller pore sizes of 20-50 nm (nanofiltration) are used. The smaller the pore size, the lower the flow rate. To achieve higher total throughput or avoid premature blockage, pre-filters might be used to protect small pore membrane filters. Some studies have shown that prions can be removed or reduced by filtration.

Membrane filters used in production processes are commonly made from materials such as mixed cellulose ester or polyethersulfone. The filtration equipment and the filters may be purchased as pre-sterilized disposable units in sealed packaging, or must be sterilized by the user, generally by autoclaving at a temperature that does not damage the fragile filter membranes. To ensure proper functioning of the filter, the membrane filters are integrity tested post-use or sometimes pre-use. A non-destructive integrity test assures the filter is undamaged, and is also a regulatory requirement enforced by agencies like the Food and Drug Administration, the European Medicines Agency, and others.

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SECTION OVERVIEW

6. 15: Chemical Antimicrobial Control

Topic hierarchy

6.15A: Effective Disinfection

6.15B: Factors that Affect Germicidal Activity of Chemicals

6.15C: Types of Disinfectants

6.15D: Biological Control of Microbes

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6.15A: Effective Disinfection

A perfect disinfectant would offer full microbiological sterilisation, without harming humans and would also be non-corrosive.

LEARNING OBJECTIVES

Describe the rationale for selecting a disinfectant and how their effectiveness is rated

Key Takeaways

Key Points

- Most modern household disinfectants contain Bitrex, an exceptionally bitter substance added to discourage ingestion, as a safety measure.
- The choice of disinfectant to be used depends on the particular situation.
- One way to compare disinfectants is to compare how well they do against a known disinfectant, such as phenol, and rate them accordingly.

Key Terms

- **non-corrosive**: That does not cause corrosion.
- **disinfectant**: A substance which kills germs and/or viruses.
- **sterilisation**: Sterilization (or sterilisation) is a term referring to any process that eliminates (removes) or kills all forms of microbial life, including transmissible agents (such as fungi, bacteria, viruses, spore forms, etc.) present on a surface, contained in a fluid, in medication, or in a compound such as biological culture media.

A perfect disinfectant would also offer complete and full microbiological sterilisation, without harming humans and useful forms of life. It would also be inexpensive and non-corrosive. Most disinfectants, however, are by nature, potentially harmful (even toxic) to humans or animals. Most modern household disinfectants contain Bitrex, an exceptionally bitter substance added to discourage ingestion, as a safety measure. Those that are used indoors should never be mixed with other cleaning products, or else chemical reactions can occur.

The choice of disinfectant depends on the particular situation. Some disinfectants have a wide spectrum and kill many different types of microorganisms, while others kill a smaller range of disease-causing organisms but are preferred for other instances (they may be non-corrosive, non-toxic, or inexpensive).

There are arguments for creating or maintaining conditions that are not conducive to bacterial survival and multiplication, rather than attempting to kill them with chemicals. Bacteria can increase in number very quickly, which enables them to evolve rapidly. Should some bacteria survive a chemical attack, they give rise to new generations composed completely of bacteria that are resistant to the particular chemical used. Under a sustained chemical attack, the surviving bacteria in successive generations are increasingly resistant to the chemical used, and ultimately the chemical is rendered ineffective. For this reason, some question the wisdom of impregnating cloths, cutting boards, and worktops in the home with bactericidal chemicals.



Figure: **Disinfection**: Disinfection of a floor using disinfectant liquid applied using a mop

One way to compare disinfectants is to compare how well they do against a known disinfectant and rate them accordingly. Phenol is the standard disinfectant, and the corresponding rating system is called the “phenol coefficient. ” The disinfectant to be tested is

compared with phenol on a standard microbe (usually Salmonella typhi or Staphylococcus aureus). Disinfectants that are more effective than phenol have a coefficient > 1. Those that are less effective have a coefficient < 1.

A less specific measurement of effectiveness is the United States Environmental Protection Agency's (EPA) classification into either high, intermediate, or low level of disinfection. High-level disinfection kills all organisms, except high levels of bacterial spores, and is effected with a chemical germicide cleared for marketing as a sterilant by the U.S. Food and Drug Administration (FDA). Intermediate-level disinfection kills mycobacteria, most viruses, and bacteria with a chemical germicide registered as a "tuberculocide" by the EPA. Low-level disinfection kills some viruses and bacteria with a chemical germicide registered as a hospital disinfectant by the EPA.

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6.15B: Factors that Affect Germicidal Activity of Chemicals

Some antiseptics are germicides, capable of destroying microbes (bacteriocidal), while others are bacteriostatic and prevent their growth.

LEARNING OBJECTIVES

Describe how antiseptics can be bacteriocidal or bacteriostatic

Key Takeaways

Key Points

- Antiseptics are antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection, sepsis, or putrefaction.
- Antibacterials are antiseptics that have the proven ability to act against bacteria.
- Antiseptics are generally distinguished from antibiotics by the latter's ability to be transported through the lymphatic system to destroy bacteria within the body, and from disinfectants, which destroy microorganisms found on non-living objects.

Key Terms

- **germicides**: Some antiseptics are true germicides, capable of destroying microbes (bacteriocidal), while others are bacteriostatic and only prevent or inhibit their growth.
- **microbes**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **antimicrobial**: An agent that destroys microbes, inhibits their growth, or prevents or counteracts their pathogenic action.

Antiseptics are antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection, sepsis, or putrefaction. Antiseptics are generally distinguished from antibiotics by the latter's ability to be transported through the lymphatic system to destroy bacteria within the body, and from disinfectants, which destroy microorganisms found on non-living objects.

Some antiseptics are true germicides, capable of destroying microbes (bacteriocidal), while others are bacteriostatic and only prevent or inhibit their growth.

Antibacterials are antiseptics that have the proven ability to act against bacteria. Microbicides that destroy virus particles are called viricides or antivirals.

Most commonly used are ethanol (60–90%), 1-propanol (60–70%), and 2-propanol/isopropanol (70–80%) or mixtures of these alcohols. They are commonly referred to as "surgical alcohol. " They are used to disinfect the skin before injections are given, often along with iodine (tincture of iodine) or some cationic surfactants (benzalkonium chloride 0.05–0.5%, chlorhexidine 0.2–4.0%, or octenidine dihydrochloride 0.1–2.0%).



Figure: **A bottle of ethanol (95%) – an antiseptic**: A bottle of ethanol (95%) – an antiseptic

Quaternary ammonium compounds include the chemicals benzalkonium chloride (BAC), cetyl trimethylammonium bromide (CTMB), cetylpyridinium chloride (Cetrim, CPC), and benzethonium chloride (BZT). Benzalkonium chloride is used in some pre-operative skin disinfectants (conc. 0.05–0.5%) and antiseptic towels. The antimicrobial activity of Quats is inactivated by anionic surfactants, such as soaps. Related disinfectants include chlorhexidine and octenidine.

Boric acid: Used in suppositories to treat yeast infections of the vagina, in eyewashes, and as an antiviral to shorten the duration of cold sore attacks. Put into creams for burns. Also common in trace amounts in eye contact solution. A triarylmethane dye still widely used as 1% ethanol solution in Eastern Europe and ex-USSR countries for treatment of small wounds and abscesses. Efficient against gram-positive bacteria.

Chlorhexidine Gluconate: A biguanidine derivative, used in concentrations of 0.5–4.0% alone or in lower concentrations in combination with other compounds, such as alcohols. Used as a skin antiseptic and to treat inflammation of the gums (gingivitis). The microbicidal action is somewhat slow, but remanent. It is a cationic surfactant, similar to Quats.

Hydrogen peroxide: Used as a 6% (20 Vols) solution to clean and deodorize wounds and ulcers. More common 3% solutions of hydrogen peroxide have been used in household first aid for scrapes, etc. However, even this less potent form is no longer recommended for typical wound care because the strong oxidization causes scar formation and increases healing time. Gentle washing with mild soap and water or rinsing a scrape with sterile saline is a better practice.

Novel iodine antiseptics containing povidone-iodine (an iodophor, complex of povidone, a water-soluble polymer, with triiodide anions I3-, containing about 10% of active iodine) are far better tolerated, don't negatively affect wound healing, and leave a deposit of active iodine, thereby creating the so-called "remnant," or persistent, effect. The great advantage of iodine antiseptics is their wide scope of antimicrobial activity, killing all principal pathogens and, given enough time, even spores, which are considered to be the most difficult form of microorganisms to be inactivated by disinfectants and antiseptics.

Mercurochrome: Not recognized as safe and effective by the U.S. Food and Drug Administration (FDA) due to concerns about its mercury content. Other obsolete organomercury antiseptics include bis-(phenylmercuric) monohydrogenborate (Famosept).

Manuka Honey: Recognized by the U.S. Food and Drug Administration (FDA) as a medical device for use in wounds and burns. Active +15 is equal to a 15% solution of phenol.

Octenidine dihydrochloride: A cationic surfactant and bis-(dihydropyridinyl)-decane derivative, used in concentrations of 0.1–2.0%. It is similar in its action to the Quats, but is of somewhat broader spectrum of activity. Octenidine is currently increasingly used in continental Europe as a QAC's and chlorhexidine (with respect to its slow action and concerns about the carcinogenic impurity 4-chloroaniline) substitute in water- or alcohol-based skin, mucosa, and wound antiseptic. In aqueous formulations, it is often potentiated with addition of 2-phenoxyethanol.

Phenol is germicidal in strong solution, inhibitory in weaker ones. Used as a "scrub" for pre-operative hand cleansing. Used in the form of a powder as an antiseptic baby powder, where it is dusted onto the navel as it heals. Also used in mouthwashes and throat lozenges, where it has a painkilling effect as well as an antiseptic one. Example: TCP. Other phenolic antiseptics include historically important, but today rarely used (sometimes in dental surgery) thymol, today obsolete hexachlorophene, still used triclosan and sodium 3,5-dibromo-4-hydroxybenzenesulfonate (Dibromol).

Antimicrobial compound suitable for clinical use in critically colonized or infected acute and chronic wounds. The physicochemical action on the bacterial envelope prevents or impedes the development of resistant bacterial strains.

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6.15C: Types of Disinfectants

There are multiple types of disinfectants, including but not limited to air disinfectants, alcohols, and oxidizing agents.

LEARNING OBJECTIVES

List the types of disinfectants available

Key Takeaways

Key Points

- Air disinfectants are typically chemical substances capable of disinfecting microorganisms suspended in the air.
- Alcohols, usually ethanol or isopropanol, are sometimes used as a disinfectant, but more often as an antiseptic.
- Oxidizing agents act by oxidizing the cell membrane of microorganisms, which results in a loss of structure and leads to cell lysis and death.

Key Terms

- **disinfectants**: Disinfectants are substances that are applied to non-living objects to destroy microorganisms that are living on the objects. Disinfectants are substances that are applied to non-living objects to destroy microorganisms that are living on the objects.
- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.
- **antiseptic**: Any substance that inhibits the growth and reproduction of microorganisms. Generally includes only those that are used on living objects (as opposed to disinfectants) and aren't transported by the lymphatic system to destroy bacteria in the body (as opposed to antibiotics).

Types of disinfectants include: Air disinfectants, Alcohols, Aldehydes, Oxidizing agents, Phenolics, Quaternary ammonium compounds, Silver, and Copper alloy surfaces.

Air Disinfectants

Air disinfectants are typically chemical substances capable of disinfecting microorganisms suspended in the air. Disinfectants are often assumed to be limited to use on surfaces, but that is not the case. In 1928, a study found that airborne microorganisms could be killed using mists of dilute bleach. An air disinfectant must be dispersed either as an aerosol or vapor at a sufficient concentration in the air to cause the number of viable infectious microorganisms to be significantly reduced.

In the 1940s and early 1950s, further studies showed inactivation of diverse bacteria, influenza virus, and *Penicillium chrysogenum* (previously *P. notatum*) mold fungus using various glycols, principally propylene glycol and triethylene glycol. In principle, these chemical substances are ideal air disinfectants because they have both high lethality to microorganisms and low mammalian toxicity.

Although glycols are effective air disinfectants in controlled laboratory environments, it is more difficult to use them effectively in real-world environments because the disinfection of air is sensitive to continuous action. Continuous action in real-world environments with outside air exchanges at door, HVAC, and window interfaces, and in the presence of materials that adsorb and remove glycols from the air, poses engineering challenges that are not critical for surface disinfection. The engineering challenges associated with creating a sufficient concentration of the glycol vapors in the air have not to date been sufficiently addressed.

Alcohol Disinfectants

Alcohols, usually ethanol or isopropanol, are sometimes used as a disinfectant, but more often as an antiseptic, the distinction being that alcohol tends to be used on living tissue rather than nonliving surfaces. These alcohols are non-corrosive but can be a fire hazard. They also have limited residual activity due to evaporation, which results in brief contact times unless the surface is submerged. They also have a limited activity in the presence of organic material.

Alcohols are most effective when combined with purified water to facilitate diffusion through the cell membrane; 100% alcohol typically denatures only external membrane proteins. A mixture of 70% ethanol or isopropanol diluted in water is effective against a wide spectrum of bacteria, though higher concentrations are often needed to disinfect wet surfaces. Additionally, high-

concentration mixtures (such as 80% ethanol + 5% isopropanol) are required to effectively inactivate lipid-enveloped viruses (such as HIV, hepatitis B, and hepatitis C). Alcohol is only partly effective against most non-enveloped viruses (such as hepatitis A), and is not at all effective against fungal and bacterial spores.

The efficacy of alcohol is enhanced when in solution with the wetting agent dodecanoic acid (coconut soap). The synergistic effect of 29.4% ethanol with dodecanoic acid is effective against a broad spectrum of bacteria, fungi, and viruses. Further testing is being performed against *Clostridium difficile* (*C. Diff*) spores using higher concentrations of ethanol and dodecanoic acid, which has been indicated to be effective with a contact time of ten minutes.

Aldehydes, such as formaldehyde and glutaraldehyde, have a wide microbiocidal activity and are sporocidal and fungicidal. They are partly inactivated by organic matter and have slight residual activity. Some bacteria have developed resistance to glutaraldehyde; it has also been found that glutaraldehyde can cause asthma and other health hazards, hence ortho-phthalaldehyde is replacing glutaraldehyde.

Oxidizing Disinfectants

Oxidizing agents act by oxidizing the cell membrane of microorganisms, which results in a loss of structure and leads to cell lysis and death. A large number of disinfectants operate in this way. Chlorine and oxygen are strong oxidizers, so their compounds figure heavily here.

Phenolics are active ingredients in some household disinfectants. They are also found in some mouthwashes and in disinfectant soap and handwashes.

Quaternary ammonium compounds (quats), such as benzalkonium chloride, are a large group of related compounds. Some concentrated formulations have been shown to be effective low-level disinfectants. Typically, quats do not exhibit effectiveness against difficult to kill non-enveloped viruses such as norovirus, rotavirus, or polio virus.

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6.15D: Biological Control of Microbes

Learning Objectives

- Describe the types of antimicrobial agents available for controlling the growth of microbes

A wide variety of chemicals called antimicrobial agents are available for controlling the growth of microbes. For example:

1. **Chemotherapeutic agents**, including antibiotics, are administered into the infected body.
2. **Disinfectants** are chemical agents used on inanimate objects to lower the level of microbes present on the object. These are not capable of sterilizing, typically because they fail to kill endospores, some viruses, and organisms such as *Mycobacteriumtuberculosis*.
3. **Antiseptics** are chemicals used on living tissue to decrease the number of microbes present in that tissue.

Disinfectants and antiseptics affect bacteria in many ways. Those that result in bacterial death are called bactericidal agents. Those causing temporary inhibition of growth are bacteriostatic agents. No single antimicrobial agent is most effective for use in all situations – different situations may call for different agents. A number of factors affect selection of the best agent for any given situation – Antimicrobial agents must be selected with specific organisms and environmental conditions in mind. Additional variables to consider in the selection of an antimicrobial agent include pH, solubility, toxicity, organic material present, and cost.

Once an agent has been selected, it is important to evaluate it's effectiveness. In evaluating the effectiveness of antimicrobial agents, the concentration, length of contact, and whether it is lethal (-cidal) or inhibiting (-static) at that concentration of exposure are the important criteria.



Figure: **Maggot therapy**: a wound cleaned by maggots (fly larvae).

Prior to the advent of antibiotics, live organisms were used directly in attempts to control microbial infections. Examples of such biological control included bacteriotherapy, bacteriophage therapy, malaria therapy, probiotics, and the use of living maggots. In all cases the organisms themselves rather than a product of their metabolism were used as the potentially curative agent. The biological control of human infections was largely restricted to the treatment of surface infections of the skin and mucous membrane. Additionally, attempts were made to alter the microflora of the human intestinal tract to favor the growth of benign or beneficial bacteria or yeasts. Modern studies suggest that the use of biological control in the treatment of human infections should be re-evaluated in the light of the increasing world-wide occurrence of antibiotic-resistant bacteria, and the opportunities provided by recent developments in gene technology.

Key Points

- Most of the examples of biologic control of microbes predate the sulphonamides and penicillin.
- Maggot therapy, although repellent by modern standards, proved to be surprisingly effective.
- Today, a wide variety of chemicals called antimicrobial agents are available for controlling the growth of microbes. These include chemotherapeutic agents, disinfectants, and antiseptics.

Key Terms

- **probiotics**: live microorganisms that may confer a health benefit on the host.
- **antibiotics**: agents that inhibit bacterial growth or kill bacteria.

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SECTION OVERVIEW

7.1: Genes

7.1A: Bacterial Genomes

7.1B: DNA Replication in Prokaryotes

7.1C: Gene Inversion

7.1D: Slipped-Strand Mispairing

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7.1A: Bacterial Genomes

Learning Objectives

- Explain the basic features of bacterial genomes

Bacterial genomes are generally smaller and less variant in size between species when compared with genomes of animals and single cell eukaryotes. Bacterial genomes can range in size anywhere from 139 kbp to 13,000 kbp. Recent advances in sequencing technology led to the discovery of a high correlation between the number of genes and the genome size of bacteria, suggesting that bacteria have relatively small amounts of junk DNA.

Studies have since shown that a large number of bacterial species have undergone genomic degradation resulting in a decrease in genome size from their ancestral state. Over the years, researchers have proposed several theories to explain the general trend of bacterial genome decay and the relatively small size of bacterial genomes. Compelling evidence indicates that the apparent degradation of bacterial genomes is owed to a deletional bias.

In prokaryotes, most of the genome (85-90%) is non-repetitive DNA, which means coding DNA mainly forms it, while non-coding regions only take a small part. Most biological entities that are more complex than a virus sometimes or always carry additional genetic material besides that which resides in their chromosomes. In some contexts, such as sequencing the genome of a pathogenic microbe, “genome” is meant to include information stored on this auxiliary material, which is carried in plasmids. In such circumstances then, “genome” describes all of the genes and information on non-coding DNA that have the potential to be present.

Amongst species of bacteria, there is relatively little variation in genome size when compared with the genome sizes of other major groups of life. Genome size is of little relevance when considering the number of functional genes in eukaryotic species. In bacteria however, the strong correlation between the number of genes and the genome size makes the size of bacterial genomes an interesting topic for research and discussion. The general trends of bacterial evolution indicate that bacteria started as free-living organisms. Evolutionary paths led some bacteria to become pathogens and symbionts.

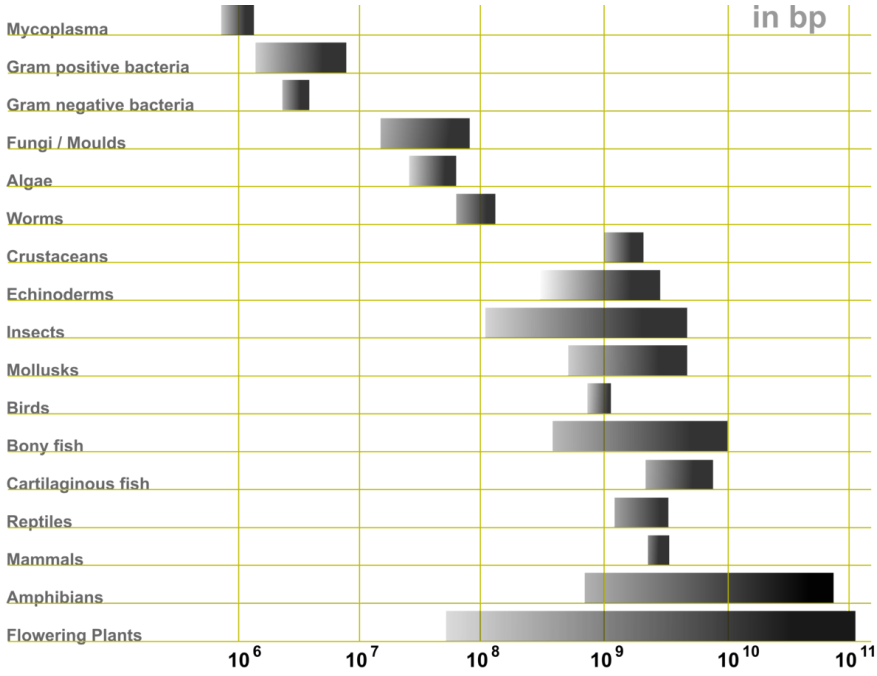

Figure 7.1A: Graph of variation in estimated genome sizes in base pairs.*: Unlike eukaryotes, bacteria show a strong correlation between genome size and number of functional genes in a genome. Genome size ranges (in base pairs) of various life forms. (CC BY-SA 4.0; Abizar).*

The lifestyles of bacteria play an integral role in their respective genome sizes. Free-living bacteria have the largest genomes out of the three types of bacteria; however, they have fewer pseudogenes than bacteria that have recently acquired pathogenicity. Facultative and recently evolved pathogenic bacteria exhibit a smaller genome size than free-living bacteria, yet they have more

pseudogenes than any other form of bacteria. Obligate bacterial symbionts or pathogens have the smallest genomes and the fewest number of pseudogenes of the three groups. The relationship between life-styles of bacteria and genome size raises questions as to the mechanisms of bacterial genome evolution.

Researchers have developed several theories to explain the patterns of genome size evolution amongst bacteria. One theory predicts that bacteria have smaller genomes due to a selective pressure on genome size to ensure faster replication. The theory is based upon the logical premise that smaller bacterial genomes will take less time to replicate. Subsequently, smaller genomes will be selected preferentially due to enhanced fitness.

Deletional bias selection is but one process involved in evolution. Two other major processes (mutation and genetic drift) can be used to explain the genome sizes of various types of bacteria.

Evidence of a deletional bias is present in the respective genome sizes of free-living bacteria, facultative and recently derived parasites and obligate parasites and symbionts. Free-living bacteria tend to have large population sizes and are subject to more opportunity for gene transfer. As such, selection can effectively operate on free-living bacteria to remove deleterious sequences resulting in a relatively small number of pseudogenes. Continually, further selective pressure is evident as free-living bacteria must produce all gene-products independent of a host. Given that there is sufficient opportunity for gene transfer to occur and there are selective pressures against even slightly deleterious deletions, it is intuitive that free-living bacteria should have the largest bacterial genomes of all bacteria types. Recently formed parasites undergo severe bottlenecks and can rely on host environments to provide gene products. As such, in recently formed and facultative parasites, there is an accumulation of pseudogenes and transposable elements due to a lack of selective pressure against deletions. The population bottlenecks reduce gene transfer and as such, deletional bias ensures the reduction of genome size in parasitic bacteria.

Key Points

- In prokaryotes, most of the genome (85-90%) is non-repetitive, coding DNA, while the remaining DNA is non-coding.
- The genome of a pathogenic microbe, “genome” is meant to include information stored on this auxiliary material, which is carried in plasmids.
- The lifestyles of bacteria play an integral role in their respective genome sizes. Free-living bacteria have the largest genomes out of the three types of bacteria; however, they have fewer pseudogenes than bacteria that have recently acquired pathogenicity.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

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7.1B: DNA Replication in Prokaryotes

Prokaryotic DNA is replicated by DNA polymerase III in the 5′ to 3′ direction at a rate of 1000 nucleotides per second.

LEARNING OBJECTIVES

Explain the functions of the enzymes involved in prokaryotic DNA replication

Key Takeaways

Key Points

- Helicase separates the DNA to form a replication fork at the origin of replication where DNA replication begins.
- Replication forks extend bi-directionally as replication continues.
- Okazaki fragments are formed on the lagging strand, while the leading strand is replicated continuously.
- DNA ligase seals the gaps between the Okazaki fragments.
- Primase synthesizes an RNA primer with a free 3′-OH, which DNA polymerase III uses to synthesize the daughter strands.

Key Terms

- **DNA replication**: a biological process occuring in all living organisms that is the basis for biological inheritance
- **helicase**: an enzyme that unwinds the DNA helix ahead of the replication machinery
- **origin of replication**: a particular sequence in a genome at which replication is initiated

DNA Replication in Prokaryotes

DNA replication employs a large number of proteins and enzymes, each of which plays a critical role during the process. One of the key players is the enzyme DNA polymerase, which adds nucleotides one by one to the growing DNA chain that are complementary to the template strand. The addition of nucleotides requires energy; this energy is obtained from the nucleotides that have three phosphates attached to them, similar to ATP which has three phosphate groups attached. When the bond between the phosphates is broken, the energy released is used to form the phosphodiester bond between the incoming nucleotide and the growing chain. In prokaryotes, three main types of polymerases are known: DNA pol I, DNA pol II, and DNA pol III. DNA pol III is the enzyme required for DNA synthesis; DNA pol I and DNA pol II are primarily required for repair.

There are specific nucleotide sequences called origins of replication where replication begins. In *E. coli*, which has a single origin of replication on its one chromosome (as do most prokaryotes), it is approximately 245 base pairs long and is rich in AT sequences. The origin of replication is recognized by certain proteins that bind to this site. An enzyme called helicase unwinds the DNA by breaking the hydrogen bonds between the nitrogenous base pairs. ATP hydrolysis is required for this process. As the DNA opens up, Y-shaped structures called replication forks are formed. Two replication forks at the origin of replication are extended bi-directionally as replication proceeds. Single-strand binding proteins coat the strands of DNA near the replication fork to prevent the single-stranded DNA from winding back into a double helix. DNA polymerase is able to add nucleotides only in the 5′ to 3′ direction (a new DNA strand can be extended only in this direction). It also requires a free 3′-OH group to which it can add nucleotides by forming a phosphodiester bond between the 3′-OH end and the 5′ phosphate of the next nucleotide. This means that it cannot add nucleotides if a free 3′-OH group is not available. Another enzyme, RNA primase, synthesizes an RNA primer that is about five to ten nucleotides long and complementary to the DNA, priming DNA synthesis. A primer provides the free 3′-OH end to start replication. DNA polymerase then extends this RNA primer, adding nucleotides one by one that are complementary to the template strand.

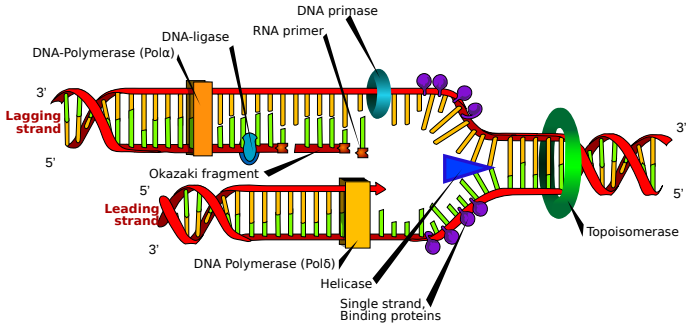

Figure: **DNA Replication in Prokaryotes**: A replication fork is formed when helicase separates the DNA strands at the origin of replication. The DNA tends to become more highly coiled ahead of the replication fork. Topoisomerase breaks and reforms DNA's phosphate backbone ahead of the replication fork, thereby relieving the pressure that results from this supercoiling. Single-strand binding proteins bind to the single-stranded DNA to prevent the helix from re-forming. Primase synthesizes an RNA primer. DNA polymerase III uses this primer to synthesize the daughter DNA strand. On the leading strand, DNA is synthesized continuously, whereas on the lagging strand, DNA is synthesized in short stretches called Okazaki fragments. DNA polymerase I replaces the RNA primer with DNA. DNA ligase seals the gaps between the Okazaki fragments, joining the fragments into a single DNA molecule.

The replication fork moves at the rate of 1000 nucleotides per second. DNA polymerase can only extend in the 5′ to 3′ direction, which poses a slight problem at the replication fork. As we know, the DNA double helix is anti-parallel; that is, one strand is in the 5′ to 3′ direction and the other is oriented in the 3′ to 5′ direction. One strand (the leading strand), complementary to the 3′ to 5′ parental DNA strand, is synthesized continuously towards the replication fork because the polymerase can add nucleotides in this direction. The other strand (the lagging strand), complementary to the 5′ to 3′ parental DNA, is extended away from the replication fork in small fragments known as Okazaki fragments, each requiring a primer to start the synthesis. Okazaki fragments are named after the Japanese scientist who first discovered them.

The leading strand can be extended by one primer alone, whereas the lagging strand needs a new primer for each of the short Okazaki fragments. The overall direction of the lagging strand will be 3′ to 5′, while that of the leading strand will be 5′ to 3′. The sliding clamp (a ring-shaped protein that binds to the DNA) holds the DNA polymerase in place as it continues to add nucleotides. Topoisomerase prevents the over-winding of the DNA double helix ahead of the replication fork as the DNA is opening up; it does so by causing temporary nicks in the DNA helix and then resealing it. As synthesis proceeds, the RNA primers are replaced by DNA. The primers are removed by the exonuclease activity of DNA pol I, while the gaps are filled in by deoxyribonucleotides. The nicks that remain between the newly-synthesized DNA (that replaced the RNA primer) and the previously-synthesized DNA are sealed by the enzyme DNA ligase that catalyzes the formation of phosphodiester linkage between the 3′-OH end of one nucleotide and the 5′ phosphate end of the other fragment.

The table summarizes the enzymes involved in prokaryotic DNA replication and the functions of each.

Prokaryotic DNA Replication: Enzymes and Their Function	
Enzyme/protein	Specific Function
DNA pol I	Exonuclease activity removes RNA primer and replaces with newly synthesized DNA
DNA pol II	Repair function
DNA pol III	Main enzyme that adds nucletides in the 5′ – 3′ direction
Helicase	Opens the DNA helix by breaking hydrogen bonds between the nitrogenous bases
Ligase	Seals the gaps between the Okazaki fragments to create one continuous DNA strand
Primase	Synthesizes RNA primers needed to start replication
Sliding Clamp	Helps to hold the DNA polymerase in place when nucleotides are being added
Topoisomerase	Helps relieve the stress on DNA when unwinding by causing breaks and then resealing the DNA

Single-strand binding proteins (SSB)	Binds to single-stranded DNA to avoid DNA rewinding back.

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7.1C: Gene Inversion

Learning Objectives

- Explain how gene sequence inversions can have a regulatory effect

Recombining sequences in site-specific reactions are usually short and occur at a single target site within the recombining sequence. For this to occur, there is typically one or more cofactors (to name a few: DNA-binding proteins and the presence or absence of DNA binding sites) and a site specific recombinase. There is also a change in orientation of the DNA that will affect gene expression or the structure of the gene product. This is done by changing the spatial arrangement of the promoter or the regulatory elements.

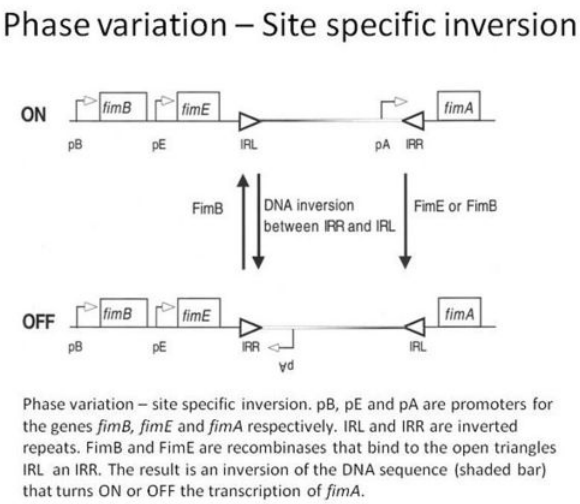

Figure: ***Phase variation Site specific Inversion****: Phase and Antigenic Variation in Bacteria. pA is the promoter for FimA, pB is the promoter for FimB and pE is the promoter for FimE. IRR is inverted repeat right and IRL is inverted repeat left. FimB and FimE are recombinases that can change the orientation of the FimA promoter by inverting the IRR and IRL.*

Through the utilization of specific recombinases, a particular DNA sequence is inverted, resulting in an ON to OFF switch, and vice versa, of the gene located within or next to this switch. Many bacterial species can utilize inversion to change the expression of certain genes for the benefit of the bacterium during infection. The inversion event can be simple by involving the toggle in expression of one gene, like *E. coli* pilin expression; or more complicated by involving multiple genes in the expression of multiple types of flagellin by *S. typhimurium*. Fimbrial adhesion by the type I fimbriae in *E. coli* undergoes site specific inversion to regulate the expression of *fimA*, the major subunit of the pili, depending on the stage of infection. The invertible element has a promoter within it that depending on the orientation will turn on or off the transcription of *fimA*. The inversion is mediated by two recombinases, FimB and FimE, and regulatory proteins H-NS, Integration Host Factor (IHF) and Leucine responsive protein (LRP). The FimE recombinase has the capability to only invert the element and turn expression from on to off, while FimB can mediate the inversion in both directions.

Key Points

- Recombining sequences in site-specific reactions are usually short and occur at a single target site. For this to occur, there is typically one or more cofactors (to name a few: DNA -binding proteins and the presence or absence of DNA binding sites) and a site specific recombinase.
- Many bacterial species can utilize inversion to change the expression of certain genes for the benefit of the bacterium during infection.
- The inversion event can be simple by involving the toggle in expression of one gene, like *E. coli* pilin expression; or more complicated by involving multiple genes in the expression of multiple types of flagellin by *S. typhimurium*.

Key Terms

- **recombinase**: Any of several enzymes that mediate recombination of DNA fragments between maternal and paternal chromosomes in prokaryotes.

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7.1D: Slipped-Strand Mispairing

Slipped strand mispairing (SSM) is a process that produces mispairing of short repeat sequences during DNA synthesis.

LEARNING OBJECTIVES

Explain how slipped-strand mispairing can be used as a mechanism to regulate gene expression

Key Takeaways

Key Points

- Altered gene expression is a result of SSM and depending where the increase or decrease of the short repeat sequences occurs in relation to the promoter will either regulate at the level of transcription or translation. The outcome is an ON or OFF phase of a gene or genes.
- SSM can result in an increase or decrease in the number of short repeat sequences. The short repeat sequences are 1 to 7 nucleotides and can be homogeneous or heterogeneous repetitive DNA sequences.
- Transcriptional regulation can occur if the repeats are located in the promoter region at the RNA polymerase binding site, -10 and -35 upstream of the gene(s).
- SSM induces transcriptional regulation is by changing the short repeat sequences located outside the promoter. If there is a change in the short repeat sequence it can affect the binding of a regulatory protein, such as an activator or repressor.

Key Terms

- **Slipped strand mispairing**: a process that produces mispairing off short repeat sequences between the mother and daughter strand during DNA synthesis.

Slipped strand mispairing (SSM) is a process that produces mispairing of short repeat sequences between the mother and daughter strand during DNA synthesis. This RecA-independent mechanism can transpire during either DNA replication or DNA repair and can be on the leading or lagging strand and can result in an increase or decrease in the number of short repeat sequences. The short repeat sequences are 1 to 7 nucleotides and can be homogeneous or heterogeneous repetitive DNA sequences.

Altered gene expression is a result of SSM and depending where the increase or decrease of the short repeat sequences occurs in relation to the promoter will either regulate at the level of transcription or translation. The outcome is an ON or OFF phase of a gene or genes.

Transcriptional regulation occurs in several ways. One possibility is if the repeats are located in the promoter region at the RNA polymerase binding site, -10 and -35, upstream of the gene(s). The opportunistic pathogen *H. influenzae* has two divergently oriented promoters in fimbriae geneshifA and hifB. The overlapping promoter regions have repeats of the dinucleotide TA in the -10 and -35 sequences. Through SSM the TA repeat region can undergo addition or subtraction of TA dinucleotides which results in the reversible ON phase or OFF phase of transcription of the hifA and hifB. The second way that SSM induces transcriptional regulation is by changing the short repeat sequences located outside the promoter. If there is a change in the short repeat sequence, it can affect the binding of a regulatory protein, such as an activator or repressor. It can also lead to differences in post-transcriptional stability of mRNA.

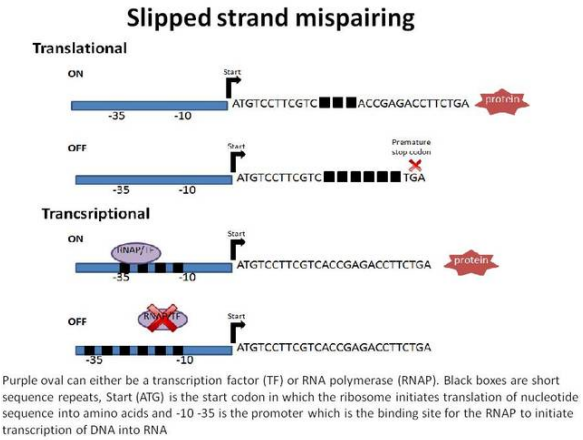

Figure: **Slip strand mispairing**: Purple ovals can either be a transcription factor (TF) or RNA polymerase (RNAP). Black boxes are short sequence repeats. Start (ATG) is the start codon in which the ribosome initiates translation of nucleotide sequence into amino acids, and (-10 -35) is the promoter which is the binding site for the RNAP to initiate transcription of DNA into RNA.

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SECTION OVERVIEW

7.2: Prokaryotic Genomes

Topic hierarchy

7.2A: Bacterial Chromosomes in the Nucleoid

7.2B: Supercoiling

7.2C: Size Variation and ORF Contents in Genomes

7.2D: Bioinformatic Analyses and Gene Distributions

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7.2A: Bacterial Chromosomes in the Nucleoid

Learning Objectives

- Evaluate the nucleoid in prokaryotes

The Nucleoid

The *nucleoid* (meaning nucleus-like) is an irregularly-shaped region within the cell of a prokaryote that contains all or most of the genetic material. In contrast to the nucleus of a eukaryotic cell, it is not surrounded by a nuclear membrane. The genome of prokaryotic organisms generally is a circular, double-stranded piece of DNA, of which multiple copies may exist at any time. The length of a genome varies widely, but is generally at least a few million base pairs.

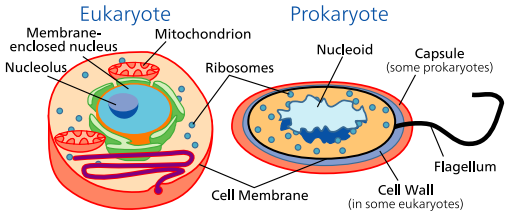

Figure: **Prokaryote cell nucleoid**: Prokaryote cell (right) showing the nucleoid in comparison to a eukaryotic cell (left) showing the nucleus.

The nucleoid can be clearly visualized on an electron micrograph at high magnification, where it is clearly visible against the cytosol. Sometimes even strands of what is thought to be DNA are visible. The nucleoid can also be seen under a light microscope.by staining it with the Feulgen stain, which specifically stains DNA. The DNA-intercalating stains DAPI and ethidium bromide are widely used for fluorescence microscopy of nucleoids.

Experimental evidence suggests that the nucleoid is largely composed of about 60% DNA, plus a small amount of RNA and protein. The latter two constituents are likely to be mainly messenger RNA and the transcription factor proteins found regulating the bacterial genome. Proteins helping to maintain the supercoiled structure of the nucleic acid are known as *nucleoid proteins* or *nucleoid-associated proteins*, and are distinct from histones of eukaryotic nuclei. In contrast to histones, the DNA-binding proteins of the nucleoid do not form nucleosomes, in which DNA is wrapped around a protein core. Instead, these proteins often use other mechanisms, such as DNA looping, to promote compaction.

The Genophore

A *genophore* is the DNA of a prokaryote. It is commonly referred to as a prokaryotic chromosome. The term “chromosome” is misleading, because the genophore lacks chromatin. The genophore is compacted through a mechanism known as supercoiling, but a chromosome is additionally compacted through the use of chromatin. The genophore is circular in most prokaryotes, and linear in very few. The circular nature of the genophore allows replication to occur without telomeres. Genophores are generally of a much smaller size than Eukaryotic chromosomes. A genophore can be as small as 580,073 base pairs (Mycoplasma genitalium). Many eukaryotes (such as plants and animals) carry genophores in organelles such as mitochondria and chloroplasts. These organelles are very similar to true prokaryotes.

Key Points

- The genome of prokaryotic organisms generally is a circular, double-stranded piece of DNA, multiple copies of which may exist at any time.
- The length of a genome varies widely, but is generally at least a few million base pairs.
- A genophore is the DNA of a prokaryote. It is commonly referred to as a prokaryotic chromosome.

Key Terms

- **nucleoid**: The irregularly-shaped region within a prokaryote cell where the genetic material is localized.
- **prokaryote**: An organism characterized by the absence of a nucleus or any other membrane-bound organelles.
- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

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7.2B: Supercoiling

Learning Objectives

- Assess the role of supercoiling in prokaryotic genomes

DNA supercoiling refers to the over- or under-winding of a DNA strand, and is an expression of the strain on that strand. Supercoiling is important in a number of biological processes, such as compacting DNA. Additionally, certain enzymes such as topoisomerases are able to change DNA topology to facilitate functions such as DNA replication or transcription. Mathematical expressions are used to describe supercoiling by comparing different coiled states to relaxed B-form DNA.

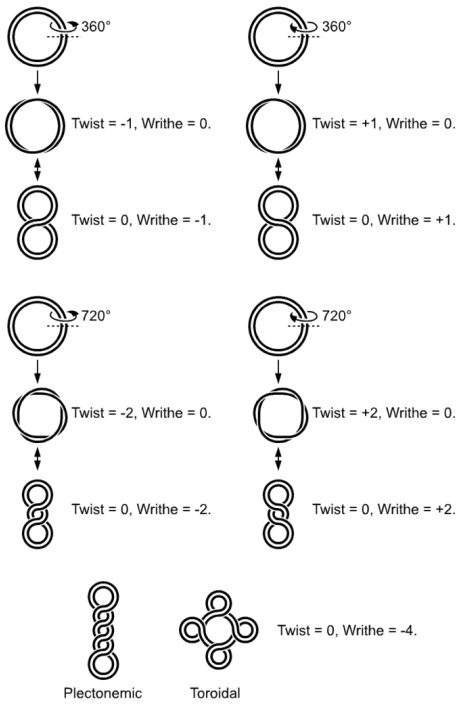

Figure: ***Supercoiled Structure of Circular DNA****: This is a supercoiled structure of circular DNA molecules with low writhe. Note that the helical nature of the DNA duplex is omitted for clarity.*

As a general rule, the DNA of most organisms is negatively supercoiled. In a "relaxed" double-helical segment of B-DNA, the two strands twist around the helical axis once every 10.4 to 10.5 base pairs of sequence. Adding or subtracting twists, as some enzymes can do, imposes strain. If a DNA segment under twist strain were closed into a circle by joining its two ends and then allowed to move freely, the circular DNA would contort into a new shape, such as a simple figure-eight. Such a contortion is a supercoil.

The simple figure eight is the simplest supercoil, and is the shape a circular DNA assumes to accommodate one too many or one too few helical twists. The two lobes of the figure eight will appear rotated either clockwise or counterclockwise with respect to one another, depending on whether the helix is over or underwound. For each additional helical twist being accommodated, the lobes will show one more rotation about their axis.

The noun form "supercoil" is rarely used in the context of DNA topology. Instead, global contortions of a circular DNA, such as the rotation of the figure-eight lobes above, are referred to as writhe. The above example illustrates that twist and writhe are interconvertible. "Supercoiling" is an abstract mathematical property representing the sum of twist and writhe. The twist is the number of helical turns in the DNA and the writhe is the number of times the double helix crosses over on itself (these are the supercoils).

Extra helical twists are positive and lead to positive supercoiling, while subtractive twisting causes negative supercoiling. Many topoisomerase enzymes sense supercoiling and either generate or dissipate it as they change DNA topology. In part because chromosomes may be very large, segments in the middle may act as if their ends are anchored. As a result, they may be unable to distribute excess twist to the rest of the chromosome or to absorb twist to recover from underwinding—the segments may become supercoiled, in other words. In response to supercoiling, they will assume an amount of writhe, just as if their ends were joined.

Supercoiled DNA forms two structures; a *plectoneme* or a *toroid*, or a combination of both. A negatively supercoiled DNA molecule will produce either a one-start left-handed helix, the toroid, or a two-start right-handed helix with terminal loops, the plectoneme. Plectonemes are typically more common in nature, and this is the shape most bacterial plasmids will take. For larger molecules, it is common for hybrid structures to form – a loop on a toroid can extend into a plectoneme. If all the loops on a toroid extend, it becomes a branch point in the plectonemic structure.

The Importance of DNA Supercoiling

DNA supercoiling is important for DNA packaging within all cells. Because the length of DNA can be thousands of times that of a cell, packaging this genetic material into the cell or nucleus (in eukaryotes) is a difficult feat. Supercoiling of DNA reduces the space and allows for much more DNA to be packaged. In prokaryotes, plectonemic supercoils are predominant, because of the circular chromosome and relatively small amount of genetic material. In eukaryotes, DNA supercoiling exists on many levels of both plectonemic and solenoidal supercoils, with the solenoidal supercoiling proving the most effective in compacting the DNA. Solenoidal supercoiling is achieved with histones to form a 10 nm fiber. This fiber is further coiled into a 30 nm fiber, and further coiled upon itself numerous times more.

DNA packaging is greatly increased during nuclear division events such as mitosis or meiosis, where DNA must be compacted and segregated to daughter cells. Condensins and cohesins are structural maintenance of chromosome (SMC) proteins that aid in the condensation of sister chromatids and the linkage of the centromere in sister chromatids. These SMC proteins induce positive supercoils.

Supercoiling is also required for DNA and RNA synthesis. Because DNA must be unwound for DNA and RNA polymerase action, supercoils will result. The region ahead of the polymerase complex will be unwound; this stress is compensated with positive supercoils ahead of the complex. Behind the complex, DNA is rewound and there will be compensatory negative supercoils. It is important to note that topoisomerases such as DNA gyrase (Type II Topoisomerase) play a role in relieving some of the stress during DNA and RNA synthesis.

Key Points

- As a general rule, the DNA of most organisms is negatively supercoiled.
- The simple figure eight is the simplest supercoil, and is the shape a circular DNA assumes to accommodate one too many or one too few helical twists.
- DNA supercoiling is important for DNA packaging within all cells.

Key Terms

- **supercoiling**: The coiling of the DNA helix upon itself; can cause disruption to transcription and lead to cell death.
- **DNA**: A biopolymer of deoxyribonucleic acids (a type of nucleic acid) that has four different chemical groups, called bases: adenine, guanine, cytosine, and thymine.
- **chromosome**: A structure in the cell nucleus that contains DNA, histone protein, and other structural proteins.

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7.2C: Size Variation and ORF Contents in Genomes

Learning Objectives

- Explain prokaryotic genome size variation and ORFs

In molecular genetics, an open reading frame (ORF) is the part of a reading frame that contains no stop codons. The transcription termination pause site is located after the ORF, beyond the translation stop codon, because if transcription were to cease before the stop codon, an incomplete protein would be made during translation.

Normally, inserts which interrupt the reading frame of a subsequent region after the start codon cause frameshift mutation of the sequence and dislocate the sequences for stop codons.

Open reading frames are used as one piece of evidence to assist in gene prediction. Long ORFs are often used, along with other evidence, to initially identify candidate protein coding regions in a DNA sequence. The presence of an ORF does not necessarily mean that the region is ever translated. For example, in a randomly generated DNA sequence with an equal percentage of each nucleotide, a stop-codon would be expected once every 21 codons. A simple gene prediction algorithm for prokaryotes might look for a start codon followed by an open reading frame that is long enough to encode a typical protein, where the codon usage of that region matches the frequency characteristic for the given organism ‘s coding regions. Even a long open reading frame by itself is not conclusive evidence for the presence of a gene.

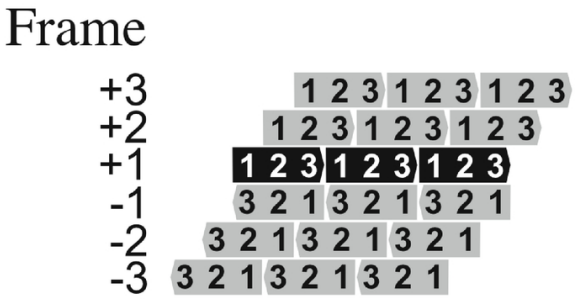

Figure: **Open Reading Frames**: Frame +1 is the ORF predicted in the database to encode a protein. +2 and +3 are the other two potential ORFs in the same strand and -1, -2, and -3 are the three potential ORFs in the antisense strand.

If a portion of a genome has been sequenced (e.g. 5′-ATCTAAAATGGGTGCC-3′), ORFs can be located by examining each of the three possible reading frames on each strand. In this sequence two out of three possible reading frames are entirely open, meaning that they do not contain a stop codon:

…A TCT AAA ATG GGT GCC…

…AT CTA AAA TGG GTG CC…

…ATC TAA AAT GGG TGC C…

Possible stop codons in DNA are “TGA”, “TAA”, and “TAG”. Thus, the last reading frame in this example contains a stop codon (TAA), unlike the first two.

Bacterial genomes display variation in size, even among strains of the same species. These microorganisms have very little noncoding or repetitive DNA, as the variation in their genome size usually reflects differences in gene repertoire. Some species, particularly bacterial parasites and symbionts, have undergone massive genome reduction and simply contain a subset of the genes present in their ancestors.

However, in free-living bacteria, such gene loss cannot explain the observed disparities in genome size because ancestral genomes would have had to contain improbably large numbers of genes. Surprisingly, a substantial fraction of the difference in gene contents in free-living bacteria is due to the presence of ORFans, that is, open reading frames (ORFs) that have no known homologs and are consequently of no known function.

The high numbers of ORFans in bacterial genomes indicate that, with the exception of those species with highly reduced genomes, much of the observed diversity in gene inventories does not result from either the loss of ancestral genes or the transfer from well-characterized organisms (processes that result in a patchy distribution of orthologs but not in unique genes) or from recent duplications (which would likely yield homologs within the same or closely related genome).

Key Points

- Open reading frames are used as one piece of evidence to assist in gene prediction.
- If a portion of a genome has been sequenced, ORFs can be located by examining each of the three possible reading frames on each strand.
- Bacterial genomes display variation in size, even among strains of the same species.

Key Terms

- **gene**: A unit of heredity; a segment of DNA or RNA that is transmitted from one generation to the next. It carries genetic information such as the sequence of amino acids for a protein.
- **codons**: The genetic code is the set of rules by which information encoded within genetic material (DNA or mRNA sequences) is translated into proteins (amino acid sequences) by living cells. Biological decoding is accomplished by the ribosome, which links amino acids in an order specified by mRNA, using transfer RNA (tRNA) molecules to carry amino acids and to read the mRNA three nucleotides at a time. The genetic code is highly similar among all organisms, and can be expressed in a simple table with 64 entries.
- **open reading frame**: A sequence of DNA triplets, between the initiator and terminator codons, that can be transcribed into mRNA and later translated into protein.

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7.2D: Bioinformatic Analyses and Gene Distributions

Bioinformatics is the study of methods for storing, retrieving and analyzing biological data.

LEARNING OBJECTIVES

Describe the purposes and applications of bioinformatics

Key Takeaways

Key Points

- The primary goal of bioinformatics is to increase the understanding of biological processes.
- Bioinformatics entails the creation and advancement of databases, algorithms, computational and statistical techniques and theory to solve problems arising from the management and analysis of biological data.
- Gene Ontology, or GO, is a major bioinformatics initiative to unify the representation of gene and gene product attributes across all species.

Key Terms

- **bioinformatics**: Bioinformatics is a branch of biological science which deals with the study of methods for storing, retrieving and analyzing biological data like nucleic acid (DNA/RNA) and protein sequence, structure, function, pathways and genetic interactions.
- **algorithms**: In mathematics and computer science, an algorithm is a step-by-step procedure for calculations. Algorithms are used for calculation, data processing, and automated reasoning.
- **gene ontology**: The Gene Ontology is a major bioinformatics initiative to unify the representation of gene and gene product attributes across all species.

Bioinformatics is a branch of biological science dealing with the study of storing, retrieving and analyzing biological data like nucleic acid (DNA/RNA) and protein sequence, structure, function, pathways and genetic interactions. It generates new knowledge that is useful in such fields as drug design and development of new software tools. Bioinformatics also deals with algorithms, databases and information systems, web technologies, artificial intelligence and soft computing, information and computation theory, structural biology, software engineering, data mining, image processing, modeling and simulation, discrete mathematics, control and system theory, circuit theory, and statistics.

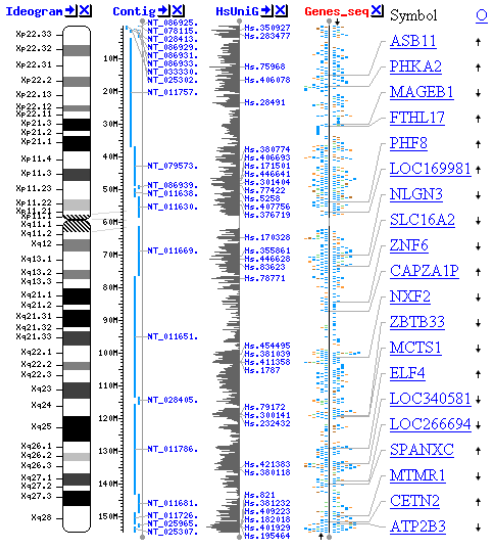

Figure: **Map of the human X chromosome**: Assembly of the human genome is one of the greatest achievements of bioinformatics

At the beginning of the “genomic revolution,” the term bioinformatics refered to the creation and maintenance of a database to store biological information like nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data. This includes nucleotide and amino acid sequences, protein domains and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:

- the development of tools that enable efficient use of various types of information
- the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets. For example, methods to locate a gene within a sequence (gene distributions), predict protein structure and/or function, and cluster protein sequences into families of related sequences.

The primary goal of bioinformatics is to increase the understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques to achieve this goal. Examples include pattern recognition, data mining, machine learning algorithms, and visualization. Major research efforts in the field include sequence alignment, gene finding, genome assembly, drug design, drug discovery, protein structure alignment, and the modeling of evolution.

Gene Ontology, or GO, is a major bioinformatics initiative to unify the representation of gene and gene product attributes across all species. More specifically, the project aims to:

- maintain and develop its controlled vocabulary of gene and gene product attributes
- annotate genes and gene products and assimilate and disseminate annotation data
- offer tools for easy access to all aspects of the data provided by the project

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SECTION OVERVIEW

7.3: DNA Replication

7.3A: Basics of DNA Replication

7.3B: DNA Replication in Eukaryotes

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7.3A: Basics of DNA Replication

DNA replication uses a semi-conservative method that results in a double-stranded DNA with one parental strand and a new daughter strand.

LEARNING OBJECTIVES

Explain how the Meselson and Stahl experiment conclusively established that DNA replication is semi-conservative.

Key Takeaways

Key Points

- There were three models suggested for DNA replication: conservative, semi-conservative, and dispersive.
- The conservative method of replication suggests that parental DNA remains together and newly-formed daughter strands are also together.
- The semi-conservative method of replication suggests that the two parental DNA strands serve as a template for new DNA and after replication, each double-stranded DNA contains one strand from the parental DNA and one new (daughter) strand.
- The dispersive method of replication suggests that, after replication, the two daughter DNAs have alternating segments of both parental and newly-synthesized DNA interspersed on both strands.
- Meselson and Stahl, using *E. coli* DNA made with two nitrogen istopes (^{14}N and ^{15}N) and density gradient centrifugation, determined that DNA replicated via the semi-conservative method of replication.

Key Terms

- **DNA replication**: a biological process occuring in all living organisms that is the basis for biological inheritance
- **isotope**: any of two or more forms of an element where the atoms have the same number of protons, but a different number of neutrons within their nuclei

Basics of DNA Replication

Watson and Crick's discovery that DNA was a two-stranded double helix provided a hint as to how DNA is replicated. During cell division, each DNA molecule has to be perfectly copied to ensure identical DNA molecules to move to each of the two daughter cells. The double-stranded structure of DNA suggested that the two strands might separate during replication with each strand serving as a template from which the new complementary strand for each is copied, generating two double-stranded molecules from one.

Models of Replication

There were three models of replication possible from such a scheme: conservative, semi-conservative, and dispersive. In conservative replication, the two original DNA strands, known as the parental strands, would re-basepair with each other after being used as templates to synthesize new strands; and the two newly-synthesized strands, known as the daughter strands, would also basepair with each other; one of the two DNA molecules after replication would be "all-old" and the other would be "all-new". In semi-conservative replication, each of the two parental DNA strands would act as a template for new DNA strands to be synthesized, but after replication, each parental DNA strand would basepair with the complementary newly-synthesized strand just synthesized, and both double-stranded DNAs would include one parental or "old" strand and one daughter or "new" strand. In dispersive replication, after replication both copies of the new DNAs would somehow have alternating segments of parental DNA and newly-synthesized DNA on each of their two strands.

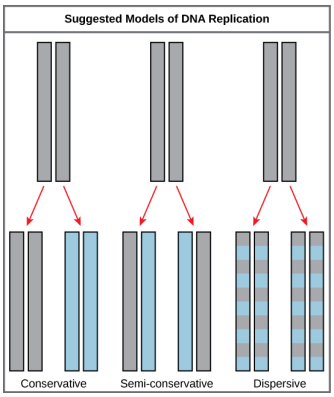

Figure: **Suggested Models of DNA Replication**: The three suggested models of DNA replication. Grey indicates the original parental DNA strands or segments and blue indicates newly-synthesized daughter DNA strands or segments.

To determine which model of replication was accurate, a seminal experiment was performed in 1958 by two researchers: Matthew Meselson and Franklin Stahl.

Meselson and Stahl

Meselson and Stahl were interested in understanding how DNA replicates. They grew *E. coli* for several generations in a medium containing a "heavy" isotope of nitrogen (^{15}N) that is incorporated into nitrogenous bases and, eventually, into the DNA. The *E. coli*culture was then shifted into medium containing the common "light" isotope of nitrogen (^{14}N) and allowed to grow for one generation. The cells were harvested and the DNA was isolated. The DNA was centrifuged at high speeds in an ultracentrifuge in a tube in which a cesium chloride density gradient had been established. Some cells were allowed to grow for one more life cycle in ^{14}N and spun again.

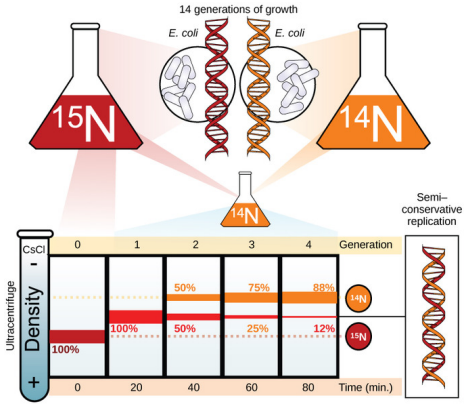

Figure: **Meselson and Stahl**: Meselson and Stahl experimented with E. coli grown first in heavy nitrogen (^{15}N) then in ligher nitrogen (^{14}N.) DNA grown in ^{15}N (red band) is heavier than DNA grown in ^{14}N (orange band) and sediments to a lower level in the cesium chloride density gradient in an ultracentrifuge. When DNA grown in ^{15}N is switched to media containing ^{14}N, after one round of cell division the DNA sediments halfway between the ^{15}N and ^{14}N levels, indicating that it now contains fifty percent ^{14}N and fifty percent ^{15}N.. In subsequent cell divisions, an increasing amount of DNA contains ^{14}N only. These data support the semi-conservative replication model.

During the density gradient ultracentrifugation, the DNA was loaded into a gradient (Meselson and Stahl used a gradient of cesium chloride salt, although other materials such as sucrose can also be used to create a gradient) and spun at high speeds of 50,000 to 60,000 rpm. In the ultracentrifuge tube, the cesium chloride salt created a density gradient, with the cesium chloride solution being more dense the farther down the tube you went. Under these circumstances, during the spin the DNA was pulled down the ultracentrifuge tube by centrifugal force until it arrived at the spot in the salt gradient where the DNA molecules' density matched that of the surrounding salt solution. At the point, the molecules stopped sedimenting and formed a stable band. By looking at the relative positions of bands of molecules run in the same gradients, you can determine the relative densities of different molecules. The molecules that form the lowest bands have the highest densities.

DNA from cells grown exclusively in ^{15}N produced a lower band than DNA from cells grown exclusively in ^{14}N. So DNA grown in ^{15}N had a higher density, as would be expected of a molecule with a heavier isotope of nitrogen incorporated into its nitrogenous bases. Meselson and Stahl noted that after one generation of growth in ^{14}N (after cells had been shifted from ^{15}N), the DNA

molecules produced only single band intermediate in position in between DNA of cells grown exclusively in ^{15}N and DNA of cells grown exclusively in ^{14}N. This suggested either a semi-conservative or dispersive mode of replication. Conservative replication would have resulted in two bands; one representing the parental DNA still with exclusively ^{15}N in its nitrogenous bases and the other representing the daughter DNA with exclusively ^{14}N in its nitrogenous bases. The single band actually seen indicated that all the DNA molecules contained equal amounts of both ^{15}N and ^{14}N.

The DNA harvested from cells grown for two generations in ^{14}N formed two bands: one DNA band was at the intermediate position between ^{15}N and ^{14}N and the other corresponded to the band of exclusively ^{14}N DNA. These results could only be explained if DNA replicates in a semi-conservative manner. Dispersive replication would have resulted in exclusively a single band in each new generation, with the band slowly moving up closer to the height of the ^{14}N DNA band. Therefore, dispersive replication could also be ruled out.

Meselson and Stahl's results established that during DNA replication, each of the two strands that make up the double helix serves as a template from which new strands are synthesized. The new strand will be complementary to the parental or "old" strand and the new strand will remain basepaired to the old strand. So each "daughter" DNA actually consists of one "old" DNA strand and one newly-synthesized strand. When two daughter DNA copies are formed, they have the identical sequences to one another and identical sequences to the original parental DNA, and the two daughter DNAs are divided equally into the two daughter cells, producing daughter cells that are genetically identical to one another and genetically identical to the parent cell.

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7.3B: DNA Replication in Eukaryotes

Learning Objectives

- Describe how DNA is replicated in eukaryotes

Because eukaryotic genomes are quite complex, DNA replication is a very complicated process that involves several enzymes and other proteins. It occurs in three main stages: initiation, elongation, and termination. DNA replication in eukaryotes occurs in three stages: initiation, elongation, and termination, which are aided by several enzymes.

Initiation

Eukaryotic DNA is bound to proteins known as histones to form structures called nucleosomes. During initiation, the DNA is made accessible to the proteins and enzymes involved in the replication process. There are specific chromosomal locations called origins of replication where replication begins. In some eukaryotes, like yeast, these locations are defined by having a specific sequence of basepairs to which the replication initiation proteins bind. In other eukaryotes, like humans, there does not appear to be a consensus sequence for their origins of replication. Instead, the replication initiation proteins might identify and bind to specific modifications to the nucleosomes in the origin region.

Certain proteins recognize and bind to the origin of replication and then allow the other proteins necessary for DNA replication to bind the same region. The first proteins to bind the DNA are said to “recruit” the other proteins. Two copies of an enzyme called helicase are among the proteins recruited to the origin. Each helicase unwinds and separates the DNA helix into single-stranded DNA. As the DNA opens up, Y-shaped structures called replication forks are formed. Because two helicases bind, two replication forks are formed at the origin of replication; these are extended in both directions as replication proceeds creating a replication bubble. There are multiple origins of replication on the eukaryotic chromosome which allow replication to occur simultaneously in hundreds to thousands of locations along each chromosome.

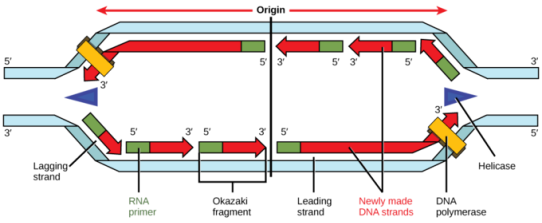


Figure: **Replication Fork Formation**: A replication fork is formed by the opening of the origin of replication; helicase separates the DNA strands. An RNA primer is synthesized by primase and is elongated by the DNA polymerase. On the leading strand, only a single RNA primer is needed, and DNA is synthesized continuously, whereas on the lagging strand, DNA is synthesized in short stretches, each of which must start with its own RNA primer. The DNA fragments are joined by DNA ligase (not shown).

Elongation

During elongation, an enzyme called DNA polymerase adds DNA nucleotides to the 3′ end of the newly synthesized polynucleotide strand. The template strand specifies which of the four DNA nucleotides (A, T, C, or G) is added at each position along the new chain. Only the nucleotide complementary to the template nucleotide at that position is added to the new strand.

DNA polymerase contains a groove that allows it to bind to a single-stranded template DNA and travel one nucleotide at at time. For example, when DNA polymerase meets an adenosine nucleotide on the template strand, it adds a thymidine to the 3′ end of the newly synthesized strand, and then moves to the next nucleotide on the template strand. This process will continue until the DNA polymerase reaches the end of the template strand.

DNA polymerase cannot initiate new strand synthesis; it only adds new nucleotides at the 3′ end of an existing strand. All newly synthesized polynucleotide strands must be initiated by a specialized RNA polymerase called primase. Primase initiates polynucleotide synthesis and by creating a short RNA polynucleotide strand complementary to template DNA strand. This short stretch of RNA nucleotides is called the primer. Once RNA primer has been synthesized at the template DNA, primase exits, and DNA polymerase extends the new strand with nucleotides complementary to the template DNA.

Eventually, the RNA nucleotides in the primer are removed and replaced with DNA nucleotides. Once DNA replication is finished, the daughter molecules are made entirely of continuous DNA nucleotides, with no RNA portions.

The Leading and Lagging Strands

DNA polymerase can only synthesize new strands in the 5′ to 3′ direction. Therefore, the two newly-synthesized strands grow in opposite directions because the template strands at each replication fork are antiparallel. The “leading strand” is synthesized continuously toward the replication fork as helicase unwinds the template double-stranded DNA.

The “lagging strand” is synthesized in the direction away from the replication fork and away from the DNA helicase unwinds. This lagging strand is synthesized in pieces because the DNA polymerase can only synthesize in the 5′ to 3′ direction, and so it constantly encounters the previously-synthesized new strand. The pieces are called Okazaki fragments, and each fragment begins with its own RNA primer.

Termination

Eukaryotic chromosomes have multiple origins of replication, which initiate replication almost simultaneously. Each origin of replication forms a bubble of duplicated DNA on either side of the origin of replication. Eventually, the leading strand of one replication bubble reaches the lagging strand of another bubble, and the lagging strand will reach the 5′ end of the previous Okazaki fragment in the same bubble.

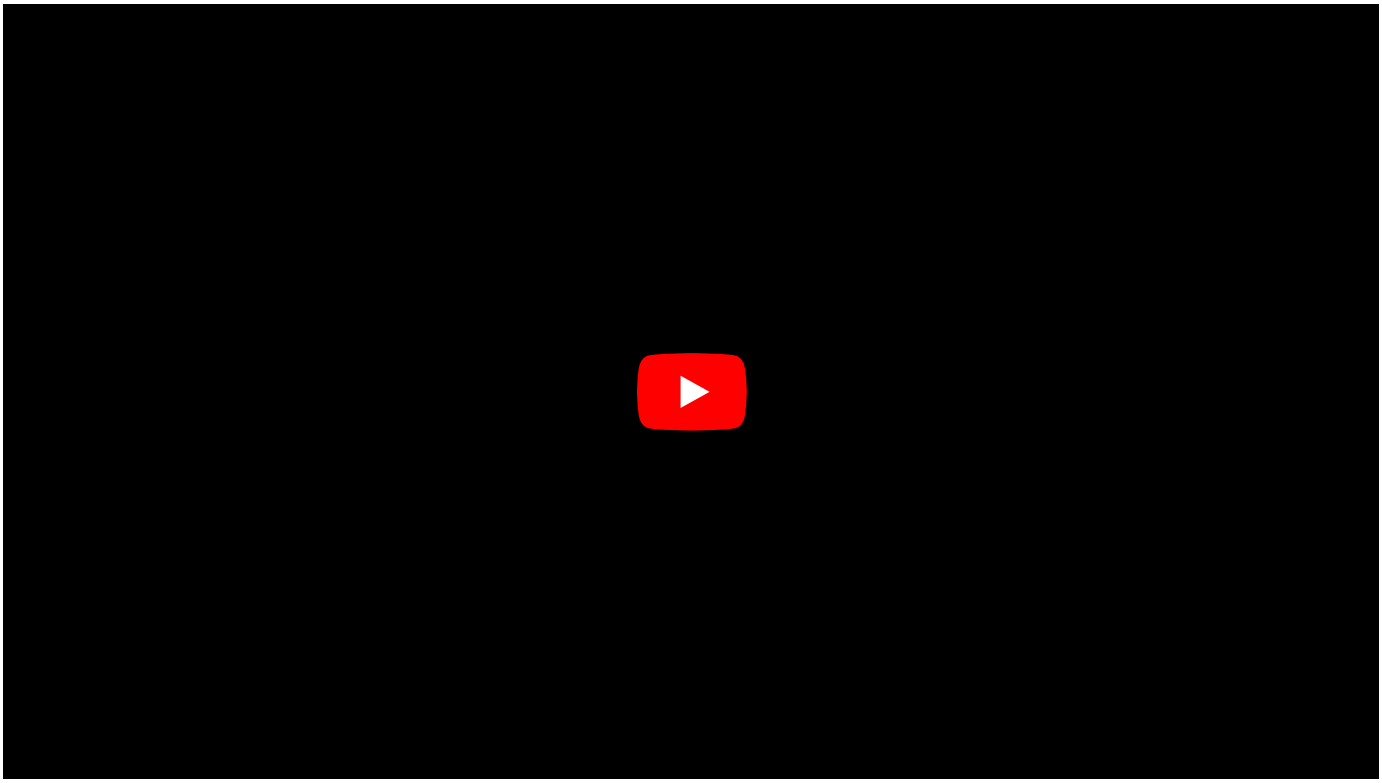
DNA polymerase halts when it reaches a section of DNA template that has already been replicated. However, DNA polymerase cannot catalyze the formation of a phosphodiester bond between the two segments of the new DNA strand, and it drops off. These unattached sections of the sugar-phosphate backbone in an

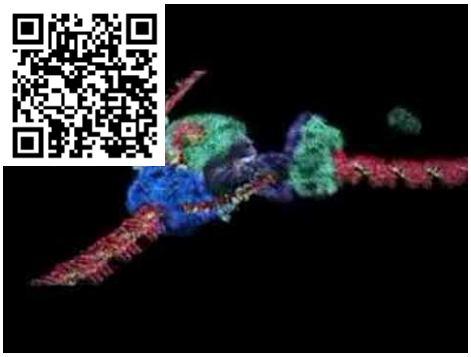
otherwise full-replicated DNA strand are called nicks.

Once all the template nucleotides have been replicated, the replication process is not yet over. RNA primers need to be replaced with DNA, and nicks in the sugar-phosphate backbone need to be connected.

The group of cellular enzymes that remove RNA primers include the proteins FEN1 (flap endonulcease 1) and RNase H. The enzymes FEN1 and RNase H remove RNA primers at the start of each leading strand and at the start of each Okazaki fragment, leaving gaps of unreplicated template DNA. Once the primers are removed, a free-floating DNA polymerase lands at the 3′ end of the preceding DNA fragment and extends the DNA over the gap. However, this creates new nicks (unconnected sugar-phosphate backbone).

In the final stage of DNA replication, the enyzme ligase joins the sugar-phosphate backbones at each nick site. After ligase has connected all nicks, the new strand is one long continuous DNA strand, and the daughter DNA molecule is complete.





DNA Replication*: This is a clip from a PBS production called "DNA: The Secret of Life." It details the latest research (as of 2005) concerning the process of DNA replication.*

Key Points

- During initiation, proteins bind to the origin of replication while helicase unwinds the DNA helix and two replication forks are formed at the origin of replication.
- During elongation, a primer sequence is added with complementary RNA nucleotides, which are then replaced by DNA nucleotides.
- During elongation the leading strand is made continuously, while the lagging strand is made in pieces called Okazaki fragments.
- During termination, primers are removed and replaced with new DNA nucleotides and the backbone is sealed by DNA ligase.

Key Terms

- **origin of replication**: a particular sequence in a genome at which replication is initiated
- **leading strand**: the template strand of the DNA double helix that is oriented so that the replication fork moves along it in the 3′ to 5′ direction

- **lagging strand**: the strand of the template DNA double helix that is oriented so that the replication fork moves along it in a 5′ to 3′ manner

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SECTION OVERVIEW

7.4: Plasmids

Topic hierarchy

7.4A: Introduction to Plasmids

7.4B: Types of Plasmids and Their Biological Significance

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7.4A: Introduction to Plasmids

Learning Objectives

- Outline the utility of plasmids

The term plasmid was first introduced by the American molecular biologist Joshua Lederberg in 1952. A plasmid is a DNA molecule that is separate from, and can replicate independently of the chromosomal DNA. They are double-stranded and, in many cases, circular. Plasmids usually occur naturally in bacteria, but are sometimes found in archaea, and even in eukaryotic organisms (e.g., the 2-micrometre ring in *Saccharomyces cerevisiae*). Plasmid sizes vary from 1 to over 1,000 kbp. The number of identical plasmids in a single cell can range anywhere from one to thousands under some circumstances. Plasmids can be considered part of the mobilome because they are often associated with conjugation, a mechanism of horizontal gene transfer.

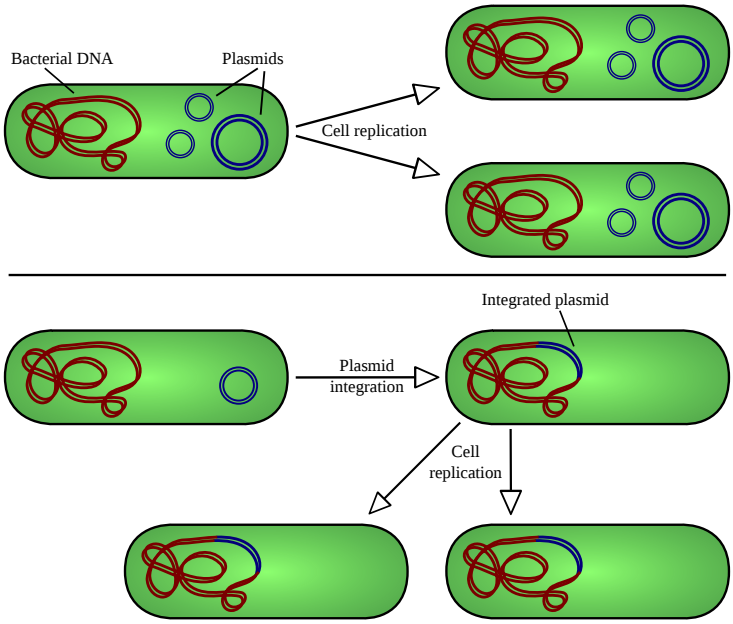

Figure: ***Step by step of cloning a gene using a plasmid****: This image shows a line drawing that compares the activity of non-integrating plasmids, on the top, with episomes, on the bottom, during cell division. The upper half of the image shows a bacterium with its chromosomal DNA and plasmids dividing into two identical bacteria, each with their chromosomal DNA and plasmids. The lower half of the image shows a bacterium with its chromosomal DNA, but with an episome. Next to this bacterium, we see the same bacterium, but after the episome has integrated into the chromosomal DNA and has become a part of it. This second bacterium now divides into two bacteria identical to it, each with an episome integrated into it.*

Plasmids are considered replicons. They can be found in all three major domains: Archaea, Bacteria, and Eukarya. Similar to viruses, plasmids are not considered by some to be a form of life. Unlike viruses, they are naked DNA and do not encode genes necessary to encase the genetic material for transfer to a new host, though some classes of plasmids encode the sex pilus necessary for their own transfer. Plasmid host-to-host transfer requires direct mechanical transfer by conjugation, or changes in incipient host gene expression allowing the intentional uptake of the genetic element by transformation. Microbial transformation with plasmid DNA is neither parasitic nor symbiotic in nature, because each implies the presence of an independent species living in a commensal or detrimental state with the host organism. Rather, plasmids provide a mechanism for horizontal gene transfer within a population of microbes and typically provide a selective advantage under a given environmental state. Plasmids may carry genes that provide resistance to naturally occurring antibiotics in a competitive environmental niche, or the proteins produced may act as toxins under similar circumstances. Plasmids can also provide bacteria with the ability to fix elemental nitrogen or to degrade recalcitrant organic compounds that provide an advantage when nutrients are scarce.

Key Points

- Plasmids can be found in all three major domains: Archaea, Bacteria, and Eukarya. Similar to viruses, plasmids are not considered by some to be a form of life.

- Plasmids provide a mechanism for horizontal gene transfer within a population of microbes and typically provide a selective advantage under a given environmental state.
- Plasmids may carry genes that provide resistance to naturally occurring antibiotics in a competitive environmental niche, or the proteins produced may act as toxins under similar circumstances.

Key Terms

- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.
- **mobilome**: The entirety of the mobile (transposable) elements of a genome.
- **replicons**: a region of DNA or RNA, that replicates from a single origin of replication.

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7.4B: Types of Plasmids and Their Biological Significance

Plasmids are commonly used to multiply (make many copies of) or express particular genes.

LEARNING OBJECTIVES

Recognize the characteristics of, and thus the functions, of plasmids

Key Takeaways

Key Points

- The gene to be replicated is inserted into copies of a plasmid containing genes that make cells resistant to particular antibiotics, and into a multiple cloning site (MCS, or polylinker), allowing the easy insertion of DNA fragments.
- A major use of plasmids is to make large amounts of proteins. Bacterium can be induced to produce large amounts of proteins from the inserted gene. This is a cheap and easy way of mass-producing a gene or the protein it then codes for; for example, insulin or even antibiotics.
- It is possible for plasmids of different types to coexist in a single cell. Several different plasmids have been found in E. coli. However, related plasmids are often incompatible, in the sense that only one of them survives in the cell line, due to the regulation of vital plasmid functions.

Key Terms

- **Col plasmids**: These plasmids contain genes that code for bacteriocins, proteins that can kill other bacteria.
- **F-plasmid**: Fertility F-plasmids contain tra genes and are capable of conjugation resulting in the expression of sex pilli.
- **Resistance plasmids**: These plasmids contain genes that provide resistance against antibiotics or poisons.

Types of Plasmids

Plasmids used in genetic engineering are called vectors. Plasmids serve as important tools in genetics and biotechnology labs, where they are commonly used to multiply (make many copies of) or express particular genes. Many plasmids are commercially available for such uses. The gene to be replicated is inserted into copies of a plasmid containing genes that make cells resistant to particular antibiotics. The gene is also inserted into a multiple cloning site (MCS, or polylinker), which is a short region containing several commonly used restriction sites allowing the easy insertion of DNA fragments.

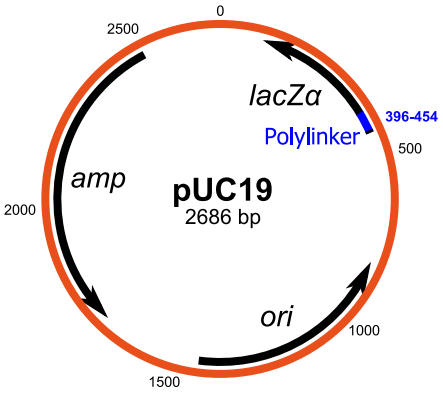

Figure: **A Plasmid Map of pUC19**: pUC19 is one of a series of plasmid cloning vectors created by Messing and co-workers in the University of California. The p in its name stands for plasmid and UC represents the University in which it was created. It is a circular double stranded DNA and has 2686 base pairs. pUC19 is one of the most widely used vector molecules as the recombinants, or the cells into which foreign DNA has been introduced, can be easily distinguished from the non-recombinants based on color differences of colonies on growth media. pUC18 is similar to pUC19, but the multiple cloning site region is reversed.

Next, the plasmids are inserted into bacteria by a process called transformation. Then, the bacteria are exposed to the particular antibiotics. Only bacteria that take up copies of the plasmid survive, since the plasmid makes them resistant. In particular, the protecting genes are expressed (used to make a protein) and the expressed protein breaks down the antibiotics. In this way, the antibiotics act as a filter, selecting only the modified bacteria. Finally, these bacteria can be grown in large amounts, harvested, and lysed (often using the alkaline lysis method) to isolate the plasmid of interest.

Another major use of plasmids is to make large amounts of proteins. In this case, researchers grow bacteria containing a plasmid harboring the gene of interest. Just as the bacterium produces proteins to confer its antibiotic resistance, it can also be induced to produce large amounts of proteins from the inserted gene. This is a cheap and easy way of mass-producing a gene or the protein it then codes for; for example, insulin or even antibiotics.

One way of grouping plasmids is by their ability to transfer to other bacteria. Conjugative plasmids contain tra genes, which perform the complex process of conjugation, the transfer of plasmids to another bacterium. Non-conjugative plasmids are incapable of initiating conjugation, hence they can be transferred only with the assistance of conjugative plasmids. An intermediate class of plasmids are mobilizable, and carry only a subset of the genes required for transfer. They can parasitize a conjugative plasmid, transferring at high frequency only in its presence. Plasmids are now being used to manipulate DNA, and may possibly be a tool for curing many diseases.

It is possible for plasmids of different types to coexist in a single cell. Several different plasmids have been found in E. coli. However, related plasmids are often incompatible, in the sense that only one of them survives in the cell line, due to the regulation of vital plasmid functions. Thus, plasmids can be assigned into incompatibility groups.

Another way to classify plasmids is by function. There are five main classes:

- Fertility F-plasmids, which contain tra genes. They are capable of conjugation and result in the expression of sex pilli.
- Resistance plasmids, which contain genes that provide resistance against antibiotics or poisons. They were historically known as R-factors, before the nature of plasmids was understood.
- Col plasmids, which contain genes that code for bacteriocins, proteins that can kill other bacteria.
- Degradative plasmids, which enable the digestion of unusual substances, e.g. toluene and salicylic acid.
- Virulence plasmids, which turn the bacterium into a pathogen.

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SECTION OVERVIEW

7.5: RNA Synthesis - Transcription

Topic hierarchy

7.5A: Elongation and Termination in Eukaryotes

7.5B: The Promoter and the Transcription Machinery

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7.5A: Elongation and Termination in Eukaryotes

Elongation synthesizes pre-mRNA in a 5′ to 3′ direction, and termination occurs in response to termination sequences and signals.

LEARNING OBJECTIVES

Describe what is happening during transcription elongation and termination

Key Takeaways

Key Points

- RNA polymerase II (RNAPII) transcribes the major share of eukaryotic genes.
- During elongation, the transcription machinery needs to move histones out of the way every time it encounters a nucleosome.
- Transcription elongation occurs in a bubble of unwound DNA, where the RNA Polymerase uses one strand of DNA as a template to catalyze the synthesis of a new RNA strand in the 5′ to 3′ direction.
- RNA Polymerase I and RNA Polymerase III terminate transcription in response to specific termination sequences in either the DNA being transcribed (RNA Polymerase I) or in the newly-synthesized RNA (RNA Polymerase III).
- RNA Polymerase II terminates transcription at random locations past the end of the gene being transcribed. The newly-synthesized RNA is cleaved at a sequence-specified location and released before transcription terminates.

Key Terms

- **nucleosome**: any of the subunits that repeat in chromatin; a coil of DNA surrounding a histone core
- **histone**: any of various simple water-soluble proteins that are rich in the basic amino acids lysine and arginine and are complexed with DNA in the nucleosomes of eukaryotic chromatin
- **chromatin**: a complex of DNA, RNA, and proteins within the cell nucleus out of which chromosomes condense during cell division

Transcription through Nucleosomes

Following the formation of the pre-initiation complex, the polymerase is released from the other transcription factors, and elongation is allowed to proceed with the polymerase synthesizing RNA in the 5′ to 3′ direction. RNA Polymerase II (RNAPII) transcribes the major share of eukaryotic genes, so this section will mainly focus on how this specific polymerase accomplishes elongation and termination.

Although the enzymatic process of elongation is essentially the same in eukaryotes and prokaryotes, the eukaryotic DNA template is more complex. When eukaryotic cells are not dividing, their genes exist as a diffuse, but still extensively packaged and compacted mass of DNA and proteins called chromatin. The DNA is tightly packaged around charged histone proteins at repeated intervals. These DNA–histone complexes, collectively called nucleosomes, are regularly spaced and include 146 nucleotides of DNA wound twice around the eight histones in a nucleosome like thread around a spool.

For polynucleotide synthesis to occur, the transcription machinery needs to move histones out of the way every time it encounters a nucleosome. This is accomplished by a special protein dimer called FACT, which stands for “facilitates chromatin transcription.” FACT partially disassembles the nucleosome immediately ahead (upstream) of a transcribing RNA Polymerase II by removing two of the eight histones (a single dimer of H2A and H2B histones is removed.) This presumably sufficiently loosens the DNA wrapped around that nucleosome so that RNA Polymerase II can transcribe through it. FACT reassembles the nucleosome behind the RNA Polymerase II by returning the missing histones to it. RNA Polymerase II will continue to elongate the newly-synthesized RNA until transcription terminates.



The FACT protein dimer allows RNA Polymerase II to transcribe through packaged DNA: DNA in eukaryotes is packaged in nucleosomes, which consist of an octomer of 4 different histone proteins. When DNA is tightly wound twice around a nucleosome, RNA Polymerase II cannot access it for transcription. FACT removes two of the histones from the nucleosome immediately ahead of RNA Polymerase, loosening the packaging so that RNA Polymerase II can continue transcription. FACT also reassembles the nucleosome immediately behindd the RNA Polymerase by returning the missing histones.

Elongation

RNA Polymerase II is a complex of 12 protein subunits. Specific subunits within the protein allow RNA Polymerase II to act as its own helicase, sliding clamp, single-stranded DNA binding protein, as well as carry out other functions. Consequently, RNA Polymerase II does not need as many accessory proteins to catalyze the synthesis of new RNA strands during transcription elongation as DNA Polymerase does to catalyze the synthesis of new DNA strands during replication elongation.

However, RNA Polymerase II does need a large collection of accessory proteins to initiate transcription at gene promoters, but once the double-stranded DNA in the transcription start region has been unwound, the RNA Polymerase II has been positioned at the +1 initiation nucleotide, and has started catalyzing new RNA strand synthesis, RNA Polymerase II clears or “escapes” the promoter region and leaves most of the transcription initiation proteins behind.

All RNA Polymerases travel along the template DNA strand in the 3′ to 5′ direction and catalyze the synthesis of new RNA strands in the 5′ to 3′ direction, adding new nucleotides to the 3′ end of the growing RNA strand.

RNA Polymerases unwind the double stranded DNA ahead of them and allow the unwound DNA behind them to rewind. As a result, RNA strand synthesis occurs in a transcription bubble of about 25 unwound DNA basebairs. Only about 8 nucleotides of newly-synthesized RNA remain basepaired to the template DNA. The rest of the RNA molecules falls off the template to allow the DNA behind it to rewind.

RNA Polymerases use the DNA strand below them as a template to direct which nucleotide to add to the 3′ end of the growing RNA strand at each point in the sequence. The RNA Polymerase travels along the template DNA one nucleotide at at time. Whichever RNA nucleotide is capable of basepairing to the template nucleotide below the RNA Polymerase is the next nucleotide to be added. Once the addition of a new nucleotide to the 3′ end of the growing strand has been catalyzed, the RNA Polymerase moves to the next DNA nucleotide on the template below it. This process continues until transcription termination occurs.

Termination



Transcription termination by RNA Polymerase II on a protein-encoding gene.: RNA Polymerase II has no specific signals that terminate its transcription. In the case of protein-encoding genes, a protein complex will bind to two locations on the growing pre-mRNA once the RNA Polymerase has transcribed past the end of the gene. CPSF in the complex will bind a AAUAAA sequence, and CstF in the complex will bind a GU-rich sequence (top figure). CPSF in the complex will cleave the pre-mRNA at a site between the two bound sequences, releasing the pre-mRNA (middle figure). Poly(A) Polymerase is a part of the same complex and will begin to add a poly-A tail to the pre-mRNA. At the same time, Xrn2 protein, which is an exonuclease, attacks the 5′ end of the RNA strand still associated with the RNA Polymerase. Xrn2 will start digesting the non-released portion of the newly synthesized RNA until Xrn2 reaches the RNA Polymerase, where it aids in displacing the RNA Polymerase from the template DNA strand. This terminates transcription at some random location downstream from the true end of the gene (bottom figure).

The termination of transcription is different for the three different eukaryotic RNA polymerases.

The ribosomal rRNA genes transcribed by RNA Polymerase I contain a specific sequence of basepairs (11 bp long in humans; 18 bp in mice) that is recognized by a termination protein called TTF-1 (Transcription Termination Factor for RNA Polymerase I.) This protein binds the DNA at its recognition sequence and blocks further transcription, causing the RNA Polymerase I to disengage from the template DNA strand and to release its newly-synthesized RNA.

The protein-encoding, structural RNA, and regulatory RNA genes transcribed by RNA Polymerse II lack any specific signals or sequences that direct RNA Polymerase II to terminate at specific locations. RNA Polymerase II can continue to transcribe RNA anywhere from a few bp to thousands of bp past the actual end of the gene. However, the transcript is cleaved at an internal site before RNA Polymerase II finishes transcribing. This releases the upstream portion of the transcript, which will serve as the initial RNA prior to further processing (the pre-mRNA in the case of protein-encoding genes.) This cleavage site is considered the “end” of the gene. The remainder of the transcript is digested by a 5′-exonuclease (called Xrn2 in humans) while it is still being transcribed by the RNA Polymerase II. When the 5′-exonulease “catches up” to RNA Polymerase II by digesting away all the overhanging RNA, it helps disengage the polymerase from its DNA template strand, finally terminating that round of transcription.

In the case of protein-encoding genes, the cleavage site which determines the “end” of the emerging pre-mRNA occurs between an upstream AAUAAA sequence and a downstream GU-rich sequence separated by about 40-60 nucleotides in the emerging RNA. Once both of these sequences have been transcribed, a protein called CPSF in humans binds the AAUAAA sequence and a protein

called CstF in humans binds the GU-rich sequence. These two proteins form the base of a complicated protein complex that forms in this region before CPSF cleaves the nascent pre-mRNA at a site 10-30 nucleotides downstream from the AAUAAA site. The Poly(A) Polymerase enzyme which catalyzes the addition of a 3′ poly-A tail on the pre-mRNA is part of the complex that forms with CPSF and CstF.

The tRNA, 5S rRNA, and structural RNAs genes transcribed by RNA Polymerase III have a not-entirely-understood termination signal. The RNAs transcribed by RNA Polymerase III have a short stretch of four to seven U's at their 3′ end. This somehow triggers RNA Polymerase III to both release the nascent RNA and disengage from the template DNA strand.

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7.5B: The Promoter and the Transcription Machinery

Learning Objectives

- Describe the role of promoters in RNA transcription

Genes are organized to make the control of gene expression easier. The promoter region is immediately upstream of the coding sequence. This region can be short (only a few nucleotides in length) or quite long (hundreds of nucleotides long). The longer the promoter, the more available space for proteins to bind. This also adds more control to the transcription process. The length of the promoter is gene-specific and can differ dramatically between genes. Consequently, the level of control of gene expression can also differ quite dramatically between genes. The purpose of the promoter is to bind transcription factors that control the initiation of transcription.

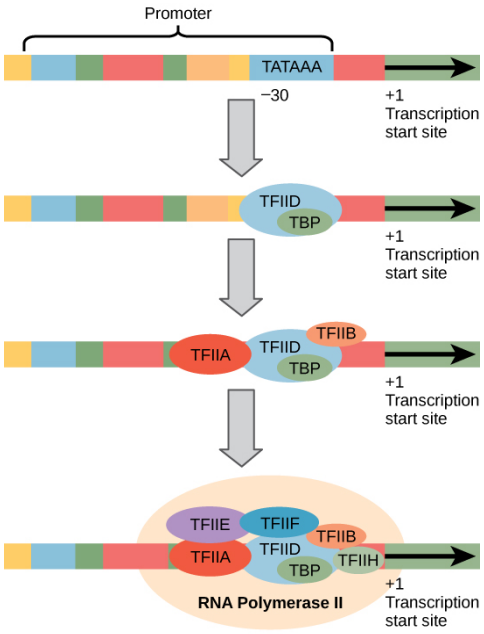

Figure: **Promoters**: A generalized promoter of a gene transcribed by RNA polymerase II is shown. Transcription factors recognize the promoter. RNA polymerase II then binds and forms the transcription initiation complex.

Within the promoter region, just upstream of the transcriptional start site, resides the TATA box. This box is simply a repeat of thymine and adenine dinucleotides (literally, TATA repeats). RNA polymerase binds to the transcription initiation complex, allowing transcription to occur. To initiate transcription, a transcription factor (TFIID) is the first to bind to the TATA box. Binding of TFIID recruits other transcription factors, including TFIIB, TFIIE, TFIIF, and TFIIH to the TATA box. Once this transcription initiation complex is assembled, RNA polymerase can bind to its upstream sequence. When bound along with the transcription factors, RNA polymerase is phosphorylated. This releases part of the protein from the DNA to activate the transcription initiation complex and places RNA polymerase in the correct orientation to begin transcription; DNA-bending protein brings the enhancer, which can be quite a distance from the gene, in contact with transcription factors and mediator proteins.

In addition to the general transcription factors, other transcription factors can bind to the promoter to regulate gene transcription. These transcription factors bind to the promoters of a specific set of genes. They are not general transcription factors that bind to every promoter complex, but are recruited to a specific sequence on the promoter of a specific gene. There are hundreds of transcription factors in a cell that each bind specifically to a particular DNA sequence motif. When transcription factors bind to the promoter just upstream of the encoded gene, they are referred to as cis-acting elements because they are on the same chromosome, just next to the gene. The region that a particular transcription factor binds to is called the transcription factor binding site. Transcription factors respond to environmental stimuli that cause the proteins to find their binding sites and initiate transcription of the gene that is needed.

Key Points

- The purpose of the promoter is to bind transcription factors that control the initiation of transcription.
- The promoter region can be short or quite long; the longer the promoter is, the more available space for proteins to bind.
- To initiate transcription, a transcription factor (TFIID) binds to the TATA box, which causes other transcription factors to subsequently bind to the TATA box.
- Once the transcription initiation complex is assembled, RNA polymerase can bind to its upstream sequence and is then phosphorylated.
- Phosphorylation of RNA polymerase releases part of the protein from the DNA to activate the transcription initiation complex and places RNA polymerase in the correct orientation to begin transcription.
- Transcription factors respond to environmental stimuli that cause the proteins to find their binding sites and initiate transcription of the gene that is needed.

Key Terms

- **TATA box**: a DNA sequence (cis-regulatory element) found in the promoter region of genes in archaea and eukaryotes
- **transcription factor**: a protein that binds to specific DNA sequences, thereby controlling the flow (or transcription) of genetic information from DNA to mRNA
- **promoter**: the section of DNA that controls the initiation of RNA transcription

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SECTION OVERVIEW

7.6: Translation: Protein Synthesis

Topic hierarchy

7.6A: Processing of tRNAs and rRNAs

7.6B: The Protein Synthesis Machinery

7.6C: Prokaryotic Transcription and Translation Are Coupled

7.6D: The Incorporation of Nonstandard Amino Acids

7.6E: Unsticking Stuck Ribosomes

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7.6A: Processing of tRNAs and rRNAs

Learning Objectives

- Describe how pre-rRNAs and pre-tRNAs are processed into mature rRNAs and tRNAs.

The tRNAs and rRNAs are structural molecules that have roles in protein synthesis; however, these RNAs are not themselves translated. In eukaryotes, pre-rRNAs are transcribed, processed, and assembled into ribosomes in the nucleolus, while pre-tRNAs are transcribed and processed in the nucleus and then released into the cytoplasm where they are linked to free amino acids for protein synthesis.

Ribosomal RNA (rRNA)

The four rRNAs in eukaryotes are first transcribed as two long precursor molecules. One contains just the pre-rRNA that will be processed into the 5S rRNA; the other spans the 28S, 5.8S, and 18S rRNAs. Enzymes then cleave the precursors into subunits corresponding to each rRNA. In bacteria, there are only three rRNAs and all are transcribed in one long precursor molecule that is cleaved into the individual rRNAs. Some of the bases of pre-rRNAs are methylated for added stability. Mature rRNAs make up 50-60% of each ribosome. Some of a ribosome's RNA molecules are purely structural, whereas others have catalytic or binding activities.

The eukaryotic ribosome is composed of two subunits: a large subunit (60S) and a small subunit (40S). The 60S subunit is composed of the 28S rRNA, 5.8S rRNA, 5S rRNA, and 50 proteins. The 40S subunit is composed of the 18S rRNA and 33 proteins. The bacterial ribosome is composed of two similar subunits, with slightly different components. The bacterial large subunit is called the 50S subunit and is composed of the 23S rRNA, 5S rRNA, and 31 proteins, while the bacterial small subunit is called the 30S subunit and is composed of the 16S rRNA and 21 proteins.

The two subunits join to constitute a functioning ribosome that is capable of creating proteins.

Transfer RNA (tRNA)

Each different tRNA binds to a specific amino acid and transfers it to the ribosome. Mature tRNAs take on a three-dimensional structure through intramolecular basepairing to position the amino acid binding site at one end and the anticodon in an unbasepaired loop of nucleotides at the other end. The anticodon is a three-nucleotide sequence, unique to each different tRNA, that interacts with a messenger RNA (mRNA) codon through complementary base pairing.

There are different tRNAs for the 21 different amino acids. Most amino acids can be carried by more than one tRNA.

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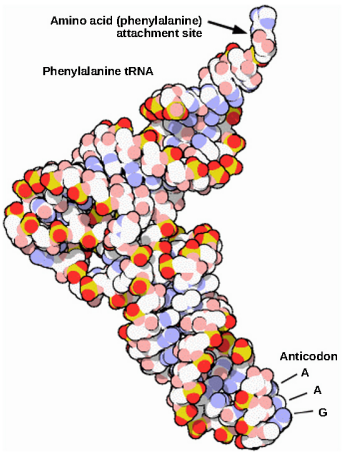

Figure: **Structure of tRNA**: This is a space-filling model of a tRNA molecule that adds the amino acid phenylalanine to a growing polypeptide chain. The anticodon AAG binds the codon UUC on the mRNA. The amino acid phenylalanine is attached to the other end of the tRNA.

In all organisms, tRNAs are transcribed in a pre-tRNA form that requires multiple processing steps before the mature tRNA is ready for use in translation. In bacteria, multiple tRNAs are often transcribed as a single RNA. The first step in their processing is

the digestion of the RNA to release individual pre-tRNAs. In archaea and eukaryotes, each pre-tRNA is transcribed as a separate transcript.

The processing to convert the pre-tRNA to a mature tRNA involves five steps.

1. The 5′ end of the pre-tRNA, called the 5′ leader sequence, is cleaved off.

2. The 3′ end of the pre-tRNA is cleaved off.

3. In all eukaryote pre-tRNAs, but in only some bacterial and archaeal pre-tRNAs, a CCA sequence of nucleotides is added to the 3′ end of the pre-tRNA after the original 3′ end is trimmed off. Some bacteria and archaea pre-tRNAs already have the CCA encoded in their transcript immediately upstream of the 3′ cleavage site, so they don't need to add one. The CCA at the 3′ end of the mature tRNA will be the site at which the tRNA's amino acid will be added.

4. Multiple nucleotides in the pre-tRNA are chemically modified, altering their nitorgen bases. On average about 12 nucleotides are modified per tRNA. The most common modifications are the conversion of adenine (A) to pseudouridine (ψ), the conversion of adenine to inosine (I), and the conversion of uridine to dihydrouridine (D). But over 100 other modifications can occur.

5. A significant number of eukaryotic and archaeal pre-tRNAs have introns that have to be spliced out. Introns are rarer in bacterial pre-tRNAs, but do occur occasionally and are spliced out.

After processing, the mature pre-tRNA is ready to have its cognate amino acid attached. The cognate amino acid for a tRNA is the one specified by its anticodon. Attaching this amino acid is called charging the tRNA. In eukaryotes, the mature tRNA is generated in the nucleus, and then exported to the cytoplasm for charging.



Processing of a pre-tRNA.: A typical pre-tRNA undergoing processing steps to generate a mature tRNA ready to have its cognate amino acid attached. Nucleotides that are cleaved away are shown in green. Chemically-modified nucleotides are in yellow, as is the CAA trinucleotide that is added to the 3′ end of the pre-tRNA during processing. The anticodon nucleotides are shown in a lighter shade of red.

Key Points

- Ribosomal RNA (rRNA) is a structural molecule that makes up over half of the mass of a ribosome and aids in protein synthesis.
- Transfer RNA (tRNA) recognizes a codon on mRNA and brings the appropriate amino acid to that site.
- rRNAs are processed from larger pre-rRNAs by trimming the larger rRNAs down and methylating some of the nucleotides.
- tRNAs are processed from pre-tRNAs by trimming both ends of the pre-tRNA, adding a CCA trinucleotide to the 3′ end, if needed, removing any introns present, and chemically modified 12 nucleotides on average per tRNA.

Key Terms

- **anticodon**: a sequence of three nucleotides in transfer RNA that binds to the complementary triplet (codon) in messenger RNA, specifying an amino acid during protein synthesis

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7.6B: The Protein Synthesis Machinery

Protein synthesis, or translation of mRNA into protein, occurs with the help of ribosomes, tRNAs, and aminoacyl tRNA synthetases.

LEARNING OBJECTIVES

Explain the role played by ribosomes, tRNA, and aminoacyl tRNA synthetases in protein synthesis

Key Takeaways

Key Points

- Ribosomes, macromolecular structures composed of rRNA and polypeptide chains, are formed of two subunits (in bacteria and archaea, 30S and 50S; in eukaryotes, 40S and 60S), that bring together mRNA and tRNAs to catalyze protein synthesis.
- Fully assembled ribosomes have three tRNA binding sites: an A site for incoming aminoacyl-tRNAs, a P site for peptidyl-tRNAs, and an E site where empty tRNAs exit.
- tRNAs (transfer ribonucleic acids), which serve to deliver the appropriate amino acid to the growing peptide chain, consist of a modified RNA chain with the appropriate amino acid covalently attached.
- tRNAs have a loop of unbasepaired nucleotides at one end of the molecule that contains three nucleotides that act as the anticodon that basepairs to the mRNA codon.
- Aminoacyl tRNA synthetases are enzymes that load the individual amino acids onto the tRNAs.

Key Terms

- **ribosome**: protein/mRNA complexes found in all cells that are involved in the production of proteins by translating messenger RNA

The Protein Synthesis Machinery

In addition to the mRNA template, many molecules and macromolecules contribute to the process of translation. The composition of each component may vary across species. For instance, ribosomes may consist of different numbers of rRNAs and polypeptides depending on the organism. However, the general structures and functions of the protein synthesis machinery are comparable from bacteria to archaea to human cells. Translation requires the input of an mRNA template, ribosomes, tRNAs, and various enzymatic factors.

Ribosomes

A ribosome is a complex macromolecule composed of structural and catalytic rRNAs, and many distinct polypeptides. In eukaryotes, the synthesis and assembly of rRNAs occurs in the nucleolus.

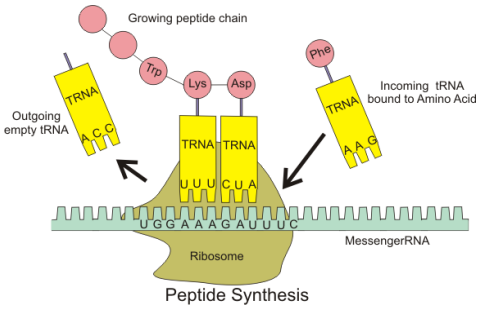

Figure: **The ribosome in action**: Structure and role of ribosomes during translation

Ribosomes exist in the cytoplasm in prokaryotes and in the cytoplasm and on rough endoplasmic reticulum membranes in eukaryotes. Mitochondria and chloroplasts also have their own ribosomes, and these look more similar to prokaryotic ribosomes (and have similar drug sensitivities) than the cytoplasmic ribosomes. Ribosomes dissociate into large and small subunits when they are not synthesizing proteins and reassociate during the initiation of translation.*E. coli* have a 30S small subunit and a 50S large subunit, for a total of 70S when assembled (recall that Svedberg units are not additive). Mammalian ribosomes have a small 40S

subunit and a large 60S subunit, for a total of 80S. The small subunit is responsible for binding the mRNA template, whereas the large subunit sequentially binds tRNAs.

In bacteria, archaea, and eukaryotes, the intact ribosome has three binding sites that accomodate tRNAs: The A site, the P site, and the E site. Incoming aminoacy-tRNAs (a tRNA with an amino acid covalently attached is called an aminoacyl-tRNA) enter the ribosome at the A site. The peptidyl-tRNA carrying the growing polypeptide chain is held in the P site. The E site holds empty tRNAs just before they exit the ribosome.

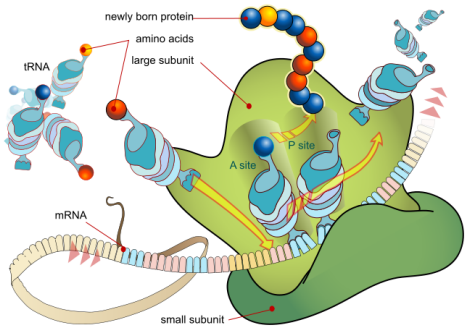

Figure: **Ribosome structure**: The large ribosomal subunit sits atop the small ribosomal subunit and the mRNA is threaded through a groove near the interface of the two subunits. The intact ribosome has three tRNA binding sites: the A site for incoming aminoacyl-tRNAs; the P site for the peptidyl-tRNA carrying the growing polypeptide chain; and the E site where empty tRNAs exit (not shown in this figure but immediately adjacent to the P site.)

Each mRNA molecule is simultaneously translated by many ribosomes, all reading the mRNA from 5′ to 3′ and synthesizing the polypeptide from the N terminus to the C terminus. The complete mRNA/poly-ribosome structure is called a polysome.

tRNAs in eukaryotes

The tRNA molecules are transcribed by RNA polymerase III. Depending on the species, 40 to 60 types of tRNAs exist in the cytoplasm. Specific tRNAs bind to codons on the mRNA template and add the corresponding amino acid to the polypeptide chain. (More accurately, the growing polypeptide chain is added to each new amino acid bound in by a tRNA.)

The transfer RNAs (tRNAs) are structural RNA molecules. In eukaryotes, tRNA mole are transcribed from tRNA genes by RNA polymerase III. Depending on the species, 40 to 60 types of tRNAs exist in the cytoplasm. Serving as adaptors, specific tRNAs bind to sequences on the mRNA template and add the corresponding amino acid to the polypeptide chain. (More accurately, the growing polypeptide chain is added to each new amino acid brought in by a tRNA.) Therefore, tRNAs are the molecules that actually “translate” the language of RNA into the language of proteins.

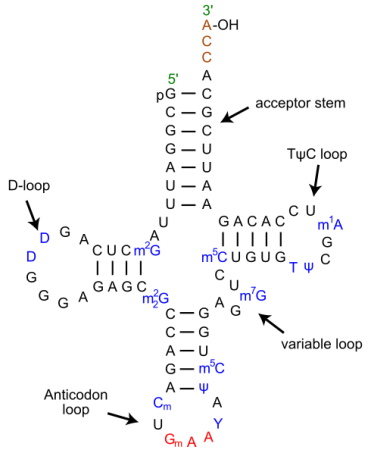

Figure: **The two-dimensional cloverleaf structure of a typical tRNA.**: All tRNAs, regardless of the species they come from or the amino acid they carry, self-basepair to produce a cloverleaf structure of four main stems and three main loops. The amino acid carried by the tRNA is covalently attached to the nucleotide at the 3′ end of the tRNA, known as the tRNA’s acceptor arm. The opposite end of the folded tRNA has the anticodon loop where the tRNA will basepair to the mRNA codon.

Of the 64 possible mRNA codons (triplet combinations of A, U, G, and C) three specify the termination of protein synthesis and 61 specify the addition of amino acids to the polypeptide chain. Of the three termination codons, one (UGA) can also be used to

encode the 21st amino acid, selenocysteine, but only if the mRNA contains a specific sequence of nucleotides known as a SECIS sequence. Of the 61 non-termination codons, one codon (AUG) also encodes the initiation of translation.

Each tRNA polynucleotide chain folds up so that some internal sections basepair with other internal sections. If just diagrammed in two dimensions, the regions where basepairing occurs are called stems, and the regions where no basepairs form are called loops, and the entire pattern of stems and loops that forms for a tRNA is called the “cloverleaf” structure. All tRNAs fold into very similar cloverleaf structures of four major stems and three major loops.

If viewed as a three-dimensional structure, all the basepaired regions of the tRNA are helical, and the tRNA folds into a L-shaped structure.

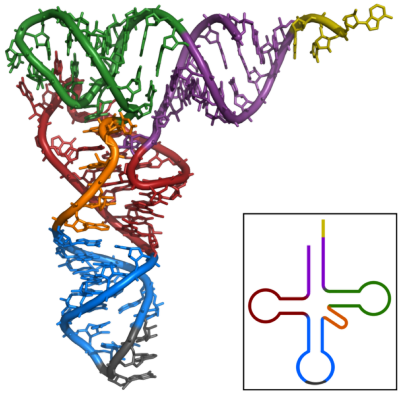

Figure: **The three dimensional shape taken by tRNAs.**: If viewed as a three-dimensional structure, all tRNAs are partially helical molecules that are vaguely L-shaped. The anticodon-containing loop is at one end of the molecule (in grey here) and the amino acid acceptor arm is at the other end of the molecule (in yellow here) past the bend of the “L”.

Each tRNA has a sequence of three nucleotides located in a loop at one end of the molecule that can basepair with an mRNA codon. This is called the tRNA’s anticodon. Each different tRNA has a different anticodon. When the tRNA anticodon basepairs with one of the mRNA codons, the tRNA will add an amino acid to a growing polypeptide chain or terminate translation, according to the genetic code. For instance, if the sequence CUA occurred on a mRNA template in the proper reading frame, it would bind a tRNA with an anticodon expressing the complementary sequence, GAU. The tRNA with this anticodon would be linked to the amino acid leucine.

Aminoacyl tRNA Synthetases

The process of pre-tRNA synthesis by RNA polymerase III only creates the RNA portion of the adaptor molecule. The corresponding amino acid must be added later, once the tRNA is processed and exported to the cytoplasm. Through the process of tRNA “charging,” each tRNA molecule is linked to its correct amino acid by a group of enzymes called aminoacyl tRNA synthetases. When an amino acid is covalently linked to a tRNA, the resulting complex is known as an aminoacyl-tRNA. At least one type of aminoacyl tRNA synthetase exists for each of the 21 amino acids; the exact number of aminoacyl tRNA synthetases varies by species. These enzymes first bind and hydrolyze ATP to catalyze the formation of a covalent bond between an amino acid and adenosine monophosphate (AMP); a pyrophosphate molecule is expelled in this reaction. This is called “activating” the amino acid. The same enzyme then catalyzes the attachment of the activated amino acid to the tRNA and the simultaneous release of AMP. After the correct amino acid covalently attached to the tRNA, it is released by the enzyme. The tRNA is said to be charged with its cognate amino acid. (the amino acid specified by its anticodon is a tRNA’s cognate amino acid.)

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7.6C: Prokaryotic Transcription and Translation Are Coupled

Learning Objectives

- Describe the events of prokaryotic transcription initiation

Overview of Prokaryotic Transcription

Prokaryotic transcription is the process in which messenger RNA transcripts of genetic material in prokaryotes are produced, to be translated for the production of proteins. Prokaryotic transcription occurs in the cytoplasm alongside translation. Prokaryotic transcription and translation can occur simultaneously. This is impossible in eukaryotes, where transcription occurs in a membrane-bound nucleus while translation occurs outside the nucleus in the cytoplasm. In prokaryotes genetic material is not enclosed in a membrane-enclosed nucleus and has access to ribosomes in the cytoplasm.

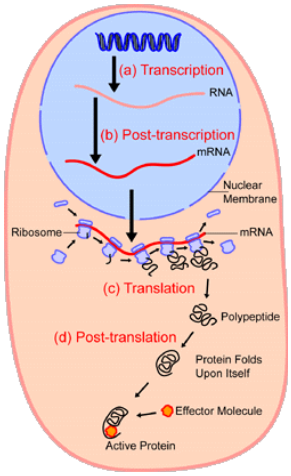

Figure: **Protein synthesis**: An overview of protein synthesis.Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active.

Transcription is controlled by a variety of regulators in prokaryotes. Many of these transcription factors are homodimers containing helix-turn-helix DNA-binding motifs.

Steps of Transcription Initiation

The following steps occur, in order, for transcription initiation:

- RNA polymerase (RNAP) binds to one of several specificity factors, σ, to form a holoenzyme. In this form, it can recognize and bind to specific promoter regions in the DNA. The -35 region and the -10 (“Pribnow box”) region comprise the basic prokaryotic promoter, and |T| stands for the terminator.
- The DNA on the template strand between the +1 site and the terminator is transcribed into RNA, which is then translated into protein. At this stage, the DNA is double-stranded (“closed”). This holoenzyme/wound-DNA structure is referred to as the closed complex.
- The DNA is unwound and becomes single-stranded (“open”) in the vicinity of the initiation site (defined as +1). This holoenzyme/unwound-DNA structure is called the open complex.
- The RNA polymerase transcribes the DNA (the beta subunit initiates the synthesis), but produces about 10 abortive (short, non-productive) transcripts which are unable to leave the RNA polymerase because the exit channel is blocked by the σ-factor.The σ-factor eventually dissociates from the holoenzyme, and elongation proceeds.

Additional Transcription Factors

Promoters can differ in “strength”; that is, how actively they promote transcription of their adjacent DNA sequence. Promoter strength is in many (but not all) cases, a matter of how tightly RNA polymerase and its associated accessory proteins bind to their

respective DNA sequences. The more similar the sequences are to a consensus sequence, the stronger the binding is.

Additional transcription regulation comes from transcription factors that can affect the stability of the holoenzyme structure at initiation. Most transcripts originate using adenosine-5′-triphosphate (ATP) and, to a lesser extent, guanosine-5′-triphosphate (GTP) (purine nucleoside triphosphates) at the +1 site. Uridine-5′-triphosphate (UTP) and cytidine-5′-triphosphate (CTP) (pyrimidine nucleoside triphosphates) are disfavoured at the initiation site.

Two termination mechanisms are well known: *Intrinsic termination* (also called Rho-independent transcription termination) involves terminator sequences within the RNA that signal the RNA polymerase to stop. The terminator sequence is usually a palindromic sequence that forms a stem-loop hairpin structure that leads to the dissociation of the RNAP from the DNA template. *Rho-dependent termination* uses a termination factor called ρ factor(rho factor) which is a protein to stop RNA synthesis at specific sites. This protein binds at a rho utilisation site on the nascent RNA strand and runs along the mRNA towards the RNAP. A stem loop structure upstream of the terminator region pauses the RNAP, when ρ-factor reaches the RNAP, it causes RNAP to dissociate from the DNA, terminating transcription.

Key Points

- In prokaryotes genetic material is not enclosed in a membrane-enclosed nucleus and has access to ribosomes in the cytoplasm.
- Transcription is known to be controlled by a variety of regulators in prokaryotes. Many of these transcription factors are homodimers containing helix-turn-helix DNA -binding motifs.
- Additional transcription regulation comes from transcription factors that can affect the stability of the holoenzyme structure at initiation.

Key Terms

- **transcription**: The synthesis of RNA under the direction of DNA.

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7.6D: The Incorporation of Nonstandard Amino Acids

Aside from the 22 standard amino acids, there are many other amino acids that are called non-proteinogenic or non-standard.

LEARNING OBJECTIVES

Describe the process and function of posttranslational modification

Key Takeaways

Key Points

- During protein synthesis, 20 different amino acids can be incorporated to become a protein.
- Posttranslational modification of amino acids change the chemical nature of an amino acid (e.g., citrullination), or make structural changes (e.g., formation of disulfide bridges).
- Non-standard amino acids either are not found in proteins (e.g., carnitine, GABA), or are not produced directly and in isolation by standard cellular machinery.

Key Terms

- **Posttranslational modification**: the chemical modification of a protein after its translation. It is one of the later steps in protein biosynthesis, and thus gene expression, for many proteins.
- **translation**: A process occurring in the ribosome, in which a strand of messenger RNA (mRNA) guides assembly of a sequence of amino acids to make a protein.
- **amino acid**: Any organic compound containing both an amino and a carboxylic acid functional group.

Posttranslational modification (PTM) is the chemical modification of a protein after its translation. It is one of the later steps in protein biosynthesis, and thus gene expression, for many proteins. A protein (also called a polypeptide) is a chain of amino acids. During protein synthesis, 20 different amino acids can be incorporated to become a protein. After translation, the posttranslational modification of amino acids extends the range of functions of the protein by attaching it to other biochemical functional groups (such as acetate, phosphate, various lipids, and carbohydrates), changing the chemical nature of an amino acid (e.g., citrullination), or making structural changes (e.g., formation of disulfide bridges).

Also, enzymes may remove amino acids from the amino end of the protein, or cut the peptide chain in the middle. For instance, the peptide hormone insulin is cut twice after disulfide bonds are formed, and a propeptide is removed from the middle of the chain; the resulting protein consists of two polypeptide chains connected by disulfide bonds. Also, most nascent polypeptides start with the amino acid methionine because the “start” codon on mRNA also codes for this amino acid. This amino acid is usually taken off during post-translational modification.

Aside from the 22 standard amino acids, there are many other amino acids that are called non-proteinogenic or non-standard. Those either are not found in proteins (e.g., carnitine, GABA), or are not produced directly and in isolation by standard cellular machinery (e.g., hydroxyproline and selenomethionine).

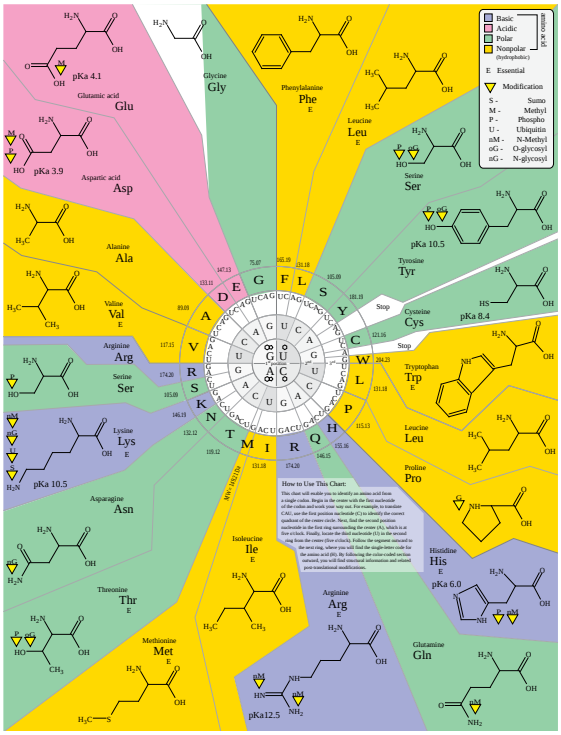

Figure: **Genetic code**: The genetic code diagram showing the amino acid residues as target of modification.

Non-standard amino acids that are found in proteins are formed by post-translational modification, which is modification after translation during protein synthesis. These modifications are often essential for the function or regulation of a protein. For example, the carboxylation of glutamate allows for better binding of calcium cations, and the hydroxylation of proline is critical for maintaining connective tissues.

Another example is the formation of hypusine in the translation initiation factor EIF5A through modification of a lysine residue. Such modifications can also determine the localization of the protein. For instance, the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane.

It is important to compare the structures of alanine and beta alanine. In alanine, the side-chain is a methyl group; in beta alanine, the side-chain contains a methylene group connected to an amino group, and the alpha carbon lacks an amino group. The two amino acids, therefore, have the same formulae but different structures.

Some nonstandard amino acids are not found in proteins. Examples include lanthionine, 2-aminoisobutyric acid, dehydroalanine, and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids. For example, ornithine and citrulline occur in the urea cycle, which is part of amino acid catabolism. A rare exception to the dominance of α-amino acids in biology is the β-amino acid beta alanine (3-aminopropanoic acid), which is used in plants and microorganisms in the synthesis of pantothenic acid (vitamin B5), a component of coenzyme A.

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7.6E: Unsticking Stuck Ribosomes

Aside from the 22 standard amino acids, there are many other amino acids that are called non-proteinogenic or non-standard.

LEARNING OBJECTIVES

Describe the process and function of posttranslational modification

Key Takeaways

Key Points

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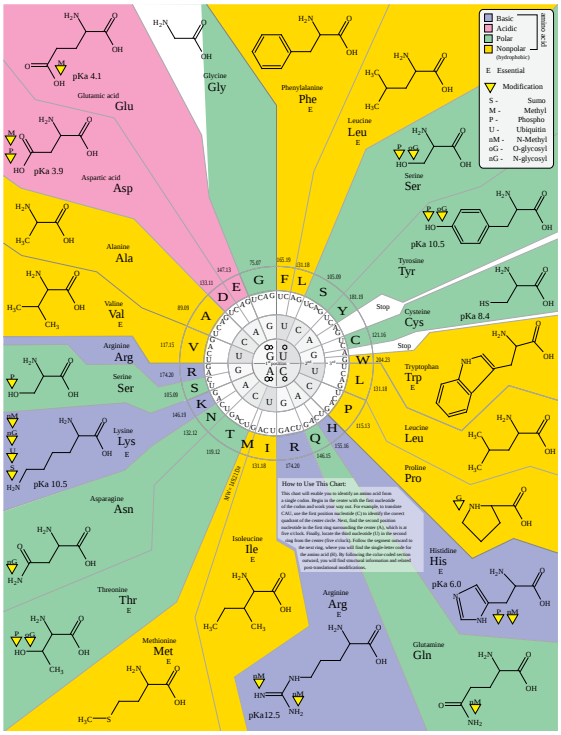

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SECTION OVERVIEW

7.7: Protein Modification, Folding, Secretion, and Degradation

Topic hierarchy

7.7A: mRNA Processing

7.7B: Denaturation and Protein Folding

7.7C: Protein Folding, Modification, and Targeting

7.7D: Regulating Protein Activity and Longevity

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7.7A: mRNA Processing

Eukaryotic pre-mRNA receives a 5′ cap and a 3′ poly (A) tail before introns are removed and the mRNA is considered ready for translation.

LEARNING OBJECTIVES

Outline the steps of pre-mRNA processing

Key Takeaways

Key Points

- A 7-methylguanosine cap is added to the 5′ end of the pre-mRNA while elongation is still in progress. The 5′ cap protects the nascent mRNA from degradation and assists in ribosome binding during translation.
- A poly (A) tail is added to the 3′ end of the pre-mRNA once elongation is complete. The poly (A) tail protects the mRNA from degradation, aids in the export of the mature mRNA to the cytoplasm, and is involved in binding proteins involved in initiating translation.
- Introns are removed from the pre-mRNA before the mRNA is exported to the cytoplasm.

Key Terms

- **intron**: a portion of a split gene that is included in pre-RNA transcripts but is removed during RNA processing and rapidly degraded
- **moiety**: a specific segment of a molecule
- **spliceosome**: a dynamic complex of RNA and protein subunits that removes introns from precursor mRNA

Pre-mRNA Processing

The eukaryotic pre-mRNA undergoes extensive processing before it is ready to be translated. The additional steps involved in eukaryotic mRNA maturation create a molecule with a much longer half-life than a prokaryotic mRNA. Eukaryotic mRNAs last for several hours, whereas the typical *E. coli* mRNA lasts no more than five seconds.

Pre-mRNAs are first coated in RNA-stabilizing proteins; these protect the pre-mRNA from degradation while it is processed and exported out of the nucleus. The three most important steps of pre-mRNA processing are the addition of stabilizing and signaling factors at the 5′ and 3′ ends of the molecule, and the removal of intervening sequences that do not specify the appropriate amino acids. In rare cases, the mRNA transcript can be “edited” after it is transcribed.

5′ Capping

While the pre-mRNA is still being synthesized, a 7-methylguanosine cap is added to the 5′ end of the growing transcript by a 5′-to-5′ phosphate linkage. This moiety protects the nascent mRNA from degradation. In addition, initiation factors involved in protein synthesis recognize the cap to help initiate translation by ribosomes.

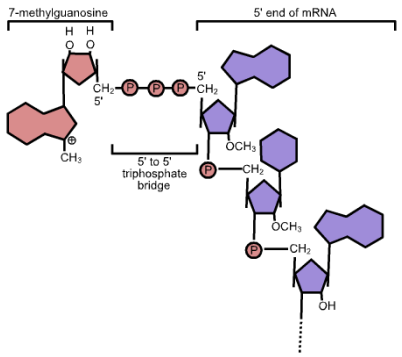

Figure: **5′ cap structure**: Capping of the pre-mRNA involves the addition of 7-methylguanosine (m^7G) to the 5′ end. The cap protects the 5′ end of the primary RNA transcript from attack by ribonucleases and is recognized by eukaryotic initiation factors involved in assembling the ribosome on the mature mRNA prior to initiating translation.

3′ Poly-A Tail

While RNA Polymerase II is still transcribing downstream of the proper end of a gene, the pre-mRNA is cleaved by an endonuclease-containing protein complex between an AAUAAA consensus sequence and a GU-rich sequence. This releases the functional pre-mRNA from the rest of the transcript, which is still attached to the RNA Polymerase. An enzyme called poly (A) polymerase (PAP) is part of the same protein complex that cleaves the pre-mRNA and it immediately adds a string of approximately 200 A nucleotides, called the poly (A) tail, to the 3′ end of the just-cleaved pre-mRNA. The poly (A) tail protects the mRNA from degradation, aids in the export of the mature mRNA to the cytoplasm, and is involved in binding proteins involved in initiating translation.



Poly (A) Polymerase adds a 3′ poly (A) tail to the pre-mRNA.: The pre-mRNA is cleaved off the rest of the growing transcript before RNA Polymerase II has stopped transcribing. This cleavage is done by an endonuclease-containing protein complex that binds to an AAUAAA sequence upstream of the cleavage site and to a GU-rich sequence downstream of the cut site. Immediately after the cleavage, Poly (A) Polymerase (PAP), which is also part of the protein complex, catalyzes the addition of up to 200 A nucleotides to the 3′ end of the just-cleaved pre-mRNA.

Pre-mRNA Splicing

Eukaryotic genes are composed of exons, which correspond to protein-coding sequences (*ex*-on signifies that they are *ex*pressed), and intervening sequences called introns (*int*-ron denotes their *int*ervening role), which may be involved in gene regulation, but are removed from the pre-mRNA during processing. Intron sequences in mRNA do not encode functional proteins.

Discovery of Introns

The discovery of introns came as a surprise to researchers in the 1970s who expected that pre-mRNAs would specify protein sequences without further processing, as they had observed in prokaryotes. The genes of higher eukaryotes very often contain one or more introns. While these regions may correspond to regulatory sequences, the biological significance of having many introns or having very long introns in a gene is unclear. It is possible that introns slow down gene expression because it takes longer to transcribe pre-mRNAs with lots of introns. Alternatively, introns may be nonfunctional sequence remnants left over from the fusion of ancient genes throughout evolution. This is supported by the fact that separate exons often encode separate protein subunits or domains. For the most part, the sequences of introns can be mutated without ultimately affecting the protein product.

Intron Processing

All introns in a pre-mRNA must be completely and precisely removed before protein synthesis. If the process errs by even a single nucleotide, the reading frame of the rejoined exons would shift, and the resulting protein would be dysfunctional. The process of removing introns and reconnecting exons is called splicing. Introns are removed and degraded while the pre-mRNA is still in the nucleus. Splicing occurs by a sequence-specific mechanism that ensures introns will be removed and exons rejoined with the accuracy and precision of a single nucleotide. The splicing of pre-mRNAs is conducted by complexes of proteins and RNA molecules called spliceosomes.

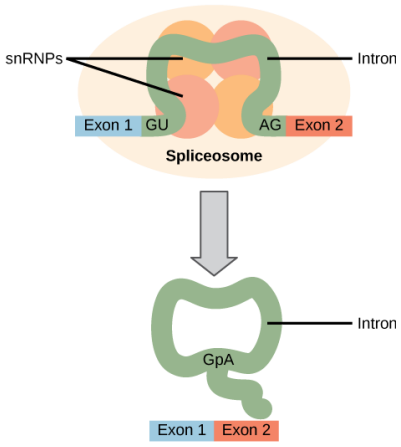

Figure: **Pre-mRNA splicing**: Pre-mRNA splicing involves the precise removal of introns from the primary RNA transcript. The splicing process is catalyzed by large complexes called spliceosomes. Each spliceosome is composed of five subunits called snRNPs. The spliceseome's actions result in the splicing together of the two exons and the release of the intron in a lariat form.

Each spliceosome is composed of five subunits called snRNPs (for small nuclear ribonucleoparticles, and pronounced "snurps".) Each snRNP is itself a complex of proteins and a special type of RNA found only in the nucleus called snRNAs (small nuclear RNAs). Spliceosomes recognize sequences at the 5′ end of the intron because introns always start with the nucleotides GU and they recognize sequences at the 3′ end of the intron because they always end with the nucleotides AG. The spliceosome cleaves the pre-mRNA's sugar phosphate backbone at the G that starts the intron and then covalently attaches that G to an internal A nucleotide within the intron. Then the spliceosme connects the 3′ end of the first exon to the 5′ end of the following exon, cleaving the 3′ end of the intron in the process. This results in the splicing together of the two exons and the release of the intron in a lariat form.

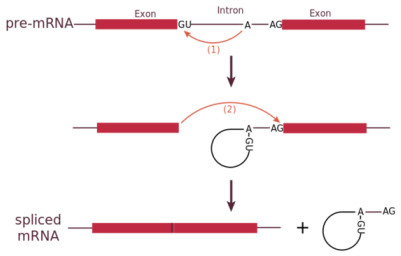

Figure: **Mechanism of pre-mRNA splicing.**: The snRNPs of the spliceosome were left out of this figure, but it shows the sites within the intron whose interactions are catalyzed by the spliceosome. Initially, the conserved G which starts an intron is cleaved from the 3′ end of the exon upstream to it and the G is covalently attached to an internal A within the intron. Then the 3′ end of the just-released exon is joined to the 5′ end of the next exon, cleaving the bond that attaches the 3′ end of the intron to its adjacent exon. This both joins the two exons and removes the intron in lariat form.

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7.7B: Denaturation and Protein Folding

Denaturation is a process in which proteins lose their shape and, therefore, their function because of changes in pH or temperature.

LEARNING OBJECTIVES

Discuss the process of protein denaturation

Key Takeaways

Key Points

- Proteins change their shape when exposed to different pH or temperatures.
- The body strictly regulates pH and temperature to prevent proteins such as enzymes from denaturing.
- Some proteins can refold after denaturation while others cannot.
- Chaperone proteins help some proteins fold into the correct shape.

Key Terms

- **chaperonin**: proteins that provide favorable conditions for the correct folding of other proteins, thus preventing aggregation
- **denaturation**: the change of folding structure of a protein (and thus of physical properties) caused by heating, changes in pH, or exposure to certain chemicals

Each protein has its own unique sequence of amino acids and the interactions between these amino acids create a specify shape. This shape determines the protein's function, from digesting protein in the stomach to carrying oxygen in the blood.

Changing the Shape of a Protein

If the protein is subject to changes in temperature, pH, or exposure to chemicals, the internal interactions between the protein's amino acids can be altered, which in turn may alter the shape of the protein. Although the amino acid sequence (also known as the protein's primary structure) does not change, the protein's shape may change so much that it becomes dysfunctional, in which case the protein is considered denatured. Pepsin, the enzyme that breaks down protein in the stomach, only operates at a very low pH. At higher pHs pepsin's conformation, the way its polypeptide chain is folded up in three dimensions, begins to change. The stomach maintains a very low pH to ensure that pepsin continues to digest protein and does not denature.

Enzymes

Because almost all biochemical reactions require enzymes, and because almost all enzymes only work optimally within relatively narrow temperature and pH ranges, many homeostatic mechanisms regulate appropriate temperatures and pH so that the enzymes can maintain the shape of their active site.

Reversing Denaturation

It is often possible to reverse denaturation because the primary structure of the polypeptide, the covalent bonds holding the amino acids in their correct sequence, is intact. Once the denaturing agent is removed, the original interactions between amino acids return the protein to its original conformation and it can resume its function.

However, denaturation can be irreversible in extreme situations, like frying an egg. The heat from a pan denatures the albumin protein in the liquid egg white and it becomes insoluble. The protein in meat also denatures and becomes firm when cooked.

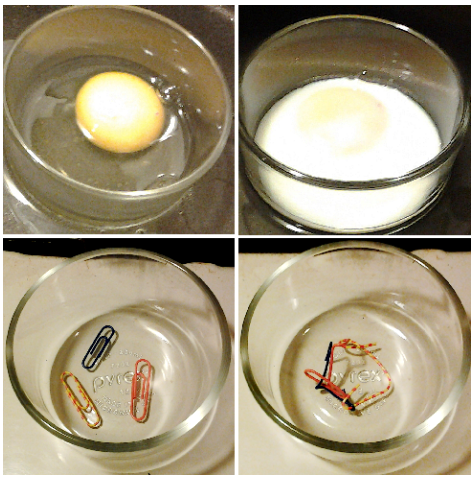

Figure: **Denaturing a protein is occasionally irreversible**: (Top) The protein albumin in raw and cooked egg white. (Bottom) A paperclip analogy visualizes the process: when cross-linked, paperclips (‘amino acids’) no longer move freely; their structure is rearranged and ‘denatured’.

Chaperone proteins (or chaperonins) are helper proteins that provide favorable conditions for protein folding to take place. The chaperonins clump around the forming protein and prevent other polypeptide chains from aggregating. Once the target protein folds, the chaperonins disassociate.

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7.7C: Protein Folding, Modification, and Targeting

In order to function, proteins must fold into the correct three-dimensional shape, and be targeted to the correct part of the cell.

LEARNING OBJECTIVES

Discuss how post-translational events affect the proper function of a protein

Key Takeaways

Key Points

- Protein folding is a process in which a linear chain of amino acids attains a defined three-dimensional structure, but there is a possibility of forming misfolded or denatured proteins, which are often inactive.
- Proteins must also be located in the correct part of the cell in order to function correctly; therefore, a signal sequence is often attached to direct the protein to its proper location, which is removed after it attains its location.
- Protein misfolding is the cause of numerous diseases, such as mad cow disease, Creutzfeldt-Jakob disease, and cystic fibrosis.

Key Terms

- **prion**: a self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue
- **chaperone**: a protein that assists the non-covalent folding/unfolding of other proteins

Protein Folding

After being translated from mRNA, all proteins start out on a ribosome as a linear sequence of amino acids. This linear sequence must “fold” during and after the synthesis so that the protein can acquire what is known as its native conformation. The native conformation of a protein is a stable three-dimensional structure that strongly determines a protein’s biological function. When a protein loses its biological function as a result of a loss of three-dimensional structure, we say that the protein has undergone denaturation. Proteins can be denatured not only by heat, but also by extremes of pH; these two conditions affect the weak interactions and the hydrogen bonds that are responsible for a protein’s three-dimensional structure. Even if a protein is properly specified by its corresponding mRNA, it could take on a completely dysfunctional shape if abnormal temperature or pH conditions prevent it from folding correctly. The denatured state of the protein does not equate with the unfolding of the protein and randomization of conformation. Actually, denatured proteins exist in a set of partially-folded states that are currently poorly understood. Many proteins fold spontaneously, but some proteins require helper molecules, called chaperones, to prevent them from aggregating during the complicated process of folding.

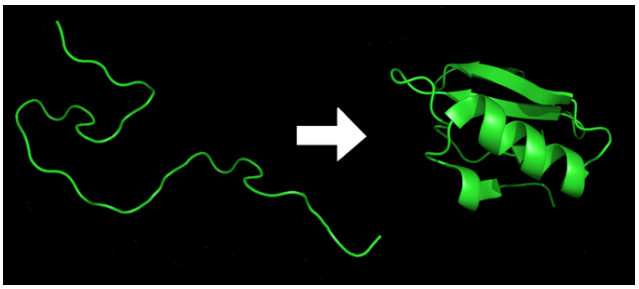

Figure: **Protein folding**: A protein starts as a linear sequence of amino acids, then folds into a 3-dimensional shape imbued with all the functional properties required inside the cell.

Protein Modification and Targeting

During and after translation, individual amino acids may be chemically modified and signal sequences may be appended to the protein. A signal sequence is a short tail of amino acids that directs a protein to a specific cellular compartment. These sequences at the amino end or the carboxyl end of the protein can be thought of as the protein’s “train ticket” to its ultimate destination. Other cellular factors recognize each signal sequence and help transport the protein from the cytoplasm to its correct compartment. For instance, a specific sequence at the amino terminus will direct a protein to the mitochondria or chloroplasts (in plants). Once the protein reaches its cellular destination, the signal sequence is usually clipped off.

Misfolding

It is very important for proteins to achieve their native conformation since failure to do so may lead to serious problems in the accomplishment of its biological function. Defects in protein folding may be the molecular cause of a range of human genetic disorders. For example, cystic fibrosis is caused by defects in a membrane-bound protein called cystic fibrosis transmembrane conductance regulator (CFTR). This protein serves as a channel for chloride ions. The most common cystic fibrosis-causing mutation is the deletion of a Phe residue at position 508 in CFTR, which causes improper folding of the protein. Many of the disease-related mutations in collagen also cause defective folding.

A misfolded protein, known as prion, appears to be the agent of a number of rare degenerative brain diseases in mammals, like the mad cow disease. Related diseases include kuru and Creutzfeldt-Jakob. The diseases are sometimes referred to as spongiform encephalopathies, so named because the brain becomes riddled with holes. Prion, the misfolded protein, is a normal constituent of brain tissue in all mammals, but its function is not yet known. Prions cannot reproduce independently and not considered living microoganisms. A complete understanding of prion diseases awaits new information about how prion protein affects brain function, as well as more detailed structural information about the protein. Therefore, improved understanding of protein folding may lead to new therapies for cystic fibrosis, Creutzfeldt-Jakob, and many other diseases.

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7.7D: Regulating Protein Activity and Longevity

A cell can rapidly change the levels of proteins in response to the environment by adding specific chemical groups to alter gene regulation.

LEARNING OBJECTIVES

Explain how chemical modifications affect protein activity and longevity

Key Takeaways

Key Points

- Proteins can be chemically modified by adding methyl, phosphate, acetyl, and ubiquitin groups.
- Protein longevity can be affected by altering stages of gene regulation, including but not limited to altering: accessibility to chromosomal DNA for transcription, rate of translation, nuclear shuttling, RNA stability, and post-translational modifications.
- Ubiquitin is added to a protein to mark it for degradation by the proteasome.

Key Terms

- **ubiquitin**: a small polypeptide present in the cells of all eukaryotes; it plays a part in modifying and degrading proteins
- **proteasome**: a complex protein, found in bacterial, archaeal and eukaryotic cells, that breaks down other proteins via proteolysis

Chemical Modifications, Protein Activity, and Longevity

Proteins can be chemically modified with the addition of methyl, phosphate, acetyl, and ubiquitin groups. The addition or removal of these groups from proteins regulates their activity or the length of time they exist in the cell. Sometimes these modifications can regulate where a protein is found in the cell; for example, in the nucleus, the cytoplasm, or attached to the plasma membrane.

Chemical modifications occur in response to external stimuli such as stress, the lack of nutrients, heat, or ultraviolet light exposure. These changes can alter protein function, epigenetic accessibility, transcription, mRNA stability, or translation; all resulting in changes in expression of various genes. This is an efficient way for the cell to rapidly change the abundance levels of specific proteins in response to the environment. Because proteins are involved in every stage of gene regulation, the phosphorylation of a protein (depending on the protein that is modified) can alter accessibility to the chromosome, can alter translation (by altering transcription factor binding or function), can change nuclear shuttling (by influencing modifications to the nuclear pore complex), can alter RNA stability (by binding or not binding to the RNA to regulate its stability), can modify translation (increase or decrease), or can change post-translational modifications (add or remove phosphates or other chemical modifications). All of these protein activities are affected by the phosphorylation process. The enzymes which are responsible for phosphorylation are known as protein kinases. The addition of a phosphate group to a protein can result in either activation or deactivation; it is protein dependent.

Another example of chemical modifications affecting protein activity include the addition or removal of methyl groups. Methyl groups are added to proteins via the process of methylation; this is the most common form of post-translational modification. The addition of methyl groups to a protein can result in protein-protein interactions that allows for transcriptional regulation, response to stress, protein repair, nuclear transport, and even differentiation processes. Methylation on side chain nitrogens is considered largely irreversible while methylation of the carboxyl groups is potentially reversible. Methylation in the proteins negates the negative charge on it and increases the hydrophobicity of the protein. Methylation on carboxylate side chains covers up a negative charge and adds hydrophobicity. The addition of this chemical group changes the property of the protein and, thus, affects it activity.

The addition of an ubiquitin group to a protein marks that protein for degradation. Ubiquitin acts like a flag indicating that the protein lifespan is complete. These proteins are moved to the proteasome, an organelle that functions to remove proteins to be degraded. One way to control gene expression is to alter the longevity of the protein: ubiquitination shortens a protein's lifespan.

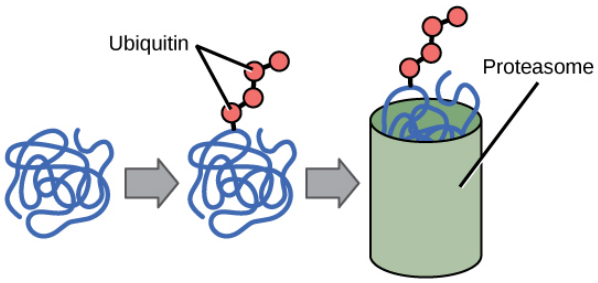

Figure: **Ubiquitin Tags**: Proteins with ubiquitin tags are marked for degradation within the proteasome.

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SECTION OVERVIEW

7.8: Archaeal Genetics

Topic hierarchy

7.8A: Chromosomes and DNA Replication in the Archaea

7.8B: Shared Features of Bacteria and Archaea

7.8C: Shared Features of Archaea and Eukaryotes

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7.8A: Chromosomes and DNA Replication in the Archaea

Archaea usually have a single circular chromosome.

LEARNING OBJECTIVES

Describe the characteristics of Archaeal chromosomes and their replication

Key Takeaways

Key Points

- Archaea are genetically distinct from bacteria and eukaryotes, with up to 15% of the proteins encoded by any one archaeal genome being unique to the domain, although most of these unique genes have no known function.
- DNA replication in archaea requires a specific primase that shares similarities to the RNA recognition motif (RRM) and to viral RNA dependent RNA polymerases.
- The circular chromosomes of archaea contain multiple origins of replication for initiation of DNA synthesis.

Key Terms

- **chromosome**: A structure in the cell nucleus that contains DNA, histone protein, and other structural proteins.
- **eukaryote**: Any of the single-celled or multicellular organisms, of the taxonomic domain Eukaryota, whose cells contain at least one distinct nucleus.
- **bacteria**: A type, species, or strain of bacterium.

Archaeal Genetics

Archaea usually have a single circular chromosome, the size of which may be as great as 5,751,492 base pairs in *Methanosarcina acetivorans*, which boasts the largest known archaean genome. One-tenth of this size is the tiny 490,885 base-pair genome of *Nanoarchaeum equitans*, which possesses the smallest archaean genome known; it is estimated to contain only 537 protein-encoding genes. Smaller independent pieces of DNA, called plasmids, are also found in archaea. Plasmids may be transferred between cells by physical contact, in a process that may be similar to bacterial conjugation.

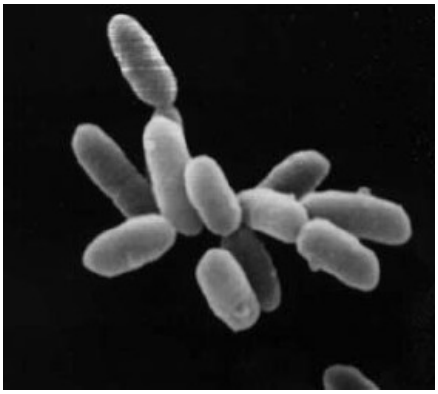

Figure: **Archaea**: Cluster of halobacterium (archaea)

Asexual Reproduction

The means of asexual reproduction that are used by Archaea include binary reproduction, multiple fission, fragmentation, or budding. The cell division process is controlled by the cell cycle; the chromosomes within the Archaea are replicated to produce two daughter chromosomes. Archaea typically have a single circular chromosome. The two daughter chromosomes are then separated and the cell divides. This process in Archaea appears to be similar to both bacterial and eukaryotic systems. The circular chromosomes contain multiple origins of replication, using DNA polymerases that resemble eukaryotic enzymes. However, the proteins involved that direct cell division are similar to those of bacterial systems.

DNA replication, similar in all systems, involves initiation, elongation, and termination. The replication of DNA, beginning at the origins of replication present on the circular chromosomes, requires initiator proteins. The recruitment of additional proteins by way of the initiator proteins allows the separation of the circular DNA and results in the formation of a bubble.

The DNA replication system in Archaea, similar to all systems, requires a free 3'OH group before synthesis is initiated. The primase used to synthesize a short RNA primer from the free 3'OH group varies in Archaea when compared to that of bacterial and eukaryotic systems. The primase used by archaea is a highly derived version of the RNA recognition motif (RRM). It is structurally similar to viral RNA dependent RNA polymerases, reverse transcriptases, cyclic nucleotide generating cyclases, and DNA polymerases involved in DNA replication and repair. Once the RNA primase has performed its job, DNA synthesis continues in a similar fashion by which the eukaryotic system and the DNA is replicated.

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7.8B: Shared Features of Bacteria and Archaea

Most of the metabolic pathways, which comprise the majority of an organism's genes, are common between Archaea and Bacteria.

LEARNING OBJECTIVES

Describe the evidence for the evolution of the Archaea from Bacteria

Key Takeaways

Key Points

- Within prokaryotes, archaeal cell structure is most similar to that of Gram-positive bacteria, largely because both have a single lipid bilayer and usually contain a thick sacculus of varying chemical composition.
- It has been proposed that the Archaea evolved from Gram-positive bacteria in response to antibiotic selection pressure.
- The evolution of Archaea in response to antibiotic selection, or any other competitive selective pressure, could also explain their adaptation to extreme environments (such as high temperature or acidity).

Key Terms

- **prokaryotes**: (/proʊkæri.oʊts/, pro-kah-ree-otes or /proʊkæriəts/, pro-kah-ree-əts) a group of organisms whose cells lack a cell nucleus (karyon), or any other membrane-bound organelles. Most prokaryotes are unicellular organisms, although a few such as myxobacteria have multicellular stages in their life cycles.
- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei that are fundamentally from bacteria.
- **bacteria**: Bacteria constitute a large domain of prokaryotic microorganisms. Typically a few micrometres in length, bacteria have a wide range of shapes, ranging from spheres to rods and spirals. Bacteria were among the first life forms to appear on Earth, and are present in most habitats on the planet.

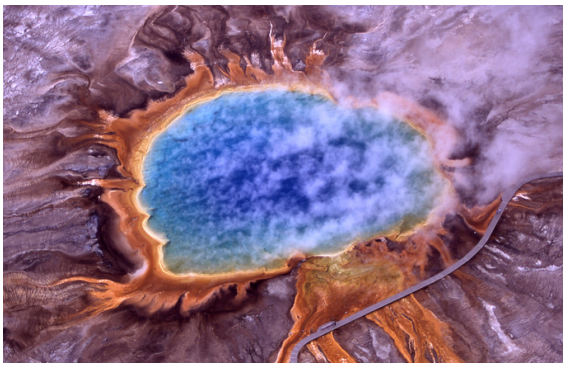

Figure: **Microbial Mats Around the Grand Prismatic Spring**: Thermophiles produce some of the bright colors of Grand Prismatic Spring, Yellowstone National Park

The relationship between the three domains is of central importance for understanding the origin of life. Most of the metabolic pathways, which comprise the majority of an organism ‘s genes, are common between Archaea and Bacteria, while most genes involved in genome expression are common between Archaea and Eukarya. Within prokaryotes, archaeal cell structure is most similar to that of Gram-positive bacteria, largely because both have a single lipid bilayer and usually contain a thick sacculus of varying chemical composition. In phylogenetic trees based upon different gene/ protein sequences of prokaryotic homologs, the archaeal homologs are more closely related to those of Gram-positive bacteria. Archaea and Gram-positive bacteria also share conserved indels in a number of important proteins, such as Hsp70 and glutamine synthetase I.

R.S. Gupta has proposed that the Archaea evolved from Gram-positive bacteria in response to antibiotic selection pressure. This is suggested by the observation that archaea are resistant to a wide variety of antibiotics that are primarily produced by Gram-positive bacteria, and that these antibiotics primarily act on the genes that distinguish Archaea from Bacteria. His proposal is that the selective pressure towards resistance generated by the Gram-positive antibiotics was eventually sufficient to cause extensive changes in many of the antibiotics' target genes, and that these strains represented the common ancestors of present-day Archaea. The evolution of Archaea in response to antibiotic selection, or any other competitive selective pressure, could also explain their adaptation to extreme environments (such as high temperature or acidity) as the result of a search for unoccupied niches to escape from antibiotic-producing organisms; Cavalier-Smith has made a similar suggestion. Gupta's proposal is also supported by other

work investigating protein structural relationships and studies that suggest that Gram-positive bacteria may constitute the earliest branching lineages within the prokaryotes.

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7.8C: Shared Features of Archaea and Eukaryotes

Archaea possess genes and several metabolic pathways that are more closely related to those of eukaryotes than prokaryotes.

LEARNING OBJECTIVES

Describe the similarities between archaea, eukaryotes, and bacteria

Key Takeaways

Key Points

- Archaea exhibit a great variety of chemical reactions in their metabolism and use many sources of energy.
- The energy released generates adenosine triphosphate (ATP) through chemiosmosis, in the same basic process that happens in the mitochondrion of eukaryotic cells.
- The chromosomes replicate from multiple starting-points (origins of replication) using DNA polymerases that resemble the equivalent eukaryotic enzymes.

Key Terms

- **eukaryote**: Any of the single-celled or multicellular organisms, of the taxonomic domain Eukaryota, whose cells contain at least one distinct nucleus.
- **mitochondrion**: a spherical or ovoid organelle found in the cytoplasm of eukaryotic cells, contains genetic material separate from that of the host; it is responsible for the conversion of food to usable energy in the form of ATP
- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei that are fundamentally from bacteria.
- **metabolism**: The complete set of chemical reactions that occur in living cells.

The evolutionary relationship between *archaea* and *eukaryotes* remains unclear. Aside from the similarities in cell structure and function that are discussed below, many genetic trees group the two.

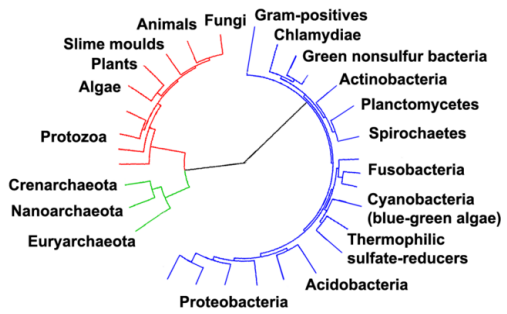

Figure: **Archaea and other domains**: Phylogenetic tree showing the relationship between the Archaea and other domains of life. Eukaryotes are colored red, archaea green and bacteria blue.

Complicating factors include claims that the relationship between eukaryotes and the archaeal phylum *Crenarchaeota* is closer than the relationship between the *Euryarchaeota*and the phylum *Crenarchaeota*, and the presence of archaean-like genes in certain bacteria, such as *Thermotoga maritima*, from horizontal gene transfer. The leading hypothesis is that the ancestor of the eukaryotes diverged early from the Archaea, and that eukaryotes arose through fusion of an archaean and eubacterium, which became the nucleus and cytoplasm. This explains various genetic similarities but runs into difficulties when it comes to explaining cell structure.

Despite this visual similarity to bacteria, archaea possess genes and several metabolic pathways that are more closely-related to those of eukaryotes, notably the enzymes involved in transcription and translation.

Archaea exhibit a great variety of chemical reactions in their metabolism and use many sources of energy. These reactions are classified into nutritional groups, depending on energy and carbon sources. Some archaea obtain energy from inorganic compounds such as sulfur or ammonia (they are lithotrophs). These include nitrifiers, methanogens and anaerobic methane oxidisers. In these reactions, one compound passes electrons to another (in a redox reaction), releasing energy to fuel the cell's activities. One

compound acts as an electron donor and another as an electron acceptor. The energy released generates adenosine triphosphate (ATP) through chemiosmosis, in the same basic process that happens in the mitochondrion of eukaryotic cells.

The chromosomes replicate from multiple starting-points (origins of replication) using DNA polymerases that resemble the equivalent eukaryotic enzymes. However, the proteins that direct cell division, such as the protein FtsZ, which forms a contracting ring around the cell, and the components of the septum that is constructed across the center of the cell, are similar to their bacterial equivalents.

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SECTION OVERVIEW

7.9: Eukaryotic Genetics

Topic hierarchy

7.9A: The Role of the Cell Cycle

7.9B: The Relationship Between Genes and Proteins

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7.9A: The Role of the Cell Cycle

The cell cycle allows multiicellular organisms to grow and divide and single-celled organisms to reproduce.

LEARNING OBJECTIVES

Explain the role of the cell cycle in carrying out the cell's essential functions

Key Takeaways

Key Points

- All multicellular organisms use cell division for growth and the maintenance and repair of cells and tissues.
- Single-celled organisms use cell division as their method of reproduction.
- Somatic cells divide regularly; all human cells (except for the cells that produce eggs and sperm) are somatic cells.
- Somatic cells contain two copies of each of their chromosomes (one copy from each parent).
- The cell cycle has two major phases: interphase and the mitotic phase.
- During interphase, the cell grows and DNA is replicated; during the mitotic phase, the replicated DNA and cytoplasmic contents are separated and the cell divides.

Key Terms

- **somatic cell**: any normal body cell of an organism that is not involved in reproduction; a cell that is not on the germline
- **interphase**: the stage in the life cycle of a cell where the cell grows and DNA is replicated
- **mitotic phase**: replicated DNA and the cytoplasmic material are divided into two identical cells

Introduction: Cell Division and Reproduction

A human, as well as every sexually-reproducing organism, begins life as a fertilized egg or zygote. Trillions of cell divisions subsequently occur in a controlled manner to produce a complex, multicellular human. In other words, that original single cell is the ancestor of every other cell in the body. Once a being is fully grown, cell reproduction is still necessary to repair or regenerate tissues. For example, new blood and skin cells are constantly being produced. All multicellular organisms use cell division for growth and the maintenance and repair of cells and tissues. Cell division is tightly regulated because the occasional failure of regulation can have life-threatening consequences. Single-celled organisms use cell division as their method of reproduction.

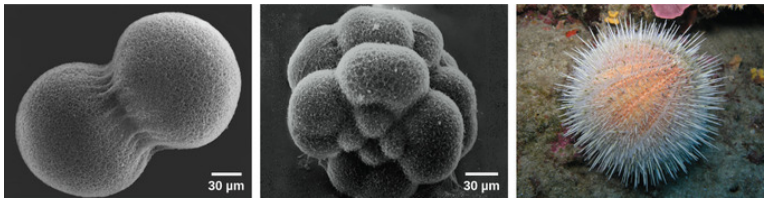

Figure: **Cell Division and Growth**: A sea urchin begins life as a single cell that (a) divides to form two cells, visible by scanning electron microscopy. After four rounds of cell division, (b) there are 16 cells, as seen in this SEM image. After many rounds of cell division, the individual develops into a complex, multicellular organism, as seen in this (c) mature sea urchin.

While there are a few cells in the body that do not undergo cell division, most somatic cells divide regularly. A somatic cell is a general term for a body cell: all human cells, except for the cells that produce eggs and sperm (which are referred to as germ cells), are somatic cells. Somatic cells contain two copies of each of their chromosomes (one copy received from each parent). Cells in the body replace themselves over the lifetime of a person. For example, the cells lining the gastrointestinal tract must be frequently replaced when constantly "worn off" by the movement of food through the gut. But what triggers a cell to divide and how does it prepare for and complete cell division?

The cell cycle is an ordered series of events involving cell growth and cell division that produces two new daughter cells. Cells on the path to cell division proceed through a series of precisely timed and carefully regulated stages of growth, DNA replication, and division that produces two identical (clone) cells. The cell cycle has two major phases: interphase and the mitotic phase. During interphase, the cell grows and DNA is replicated. During the mitotic phase, the replicated DNA and cytoplasmic contents are separated and the cell divides.

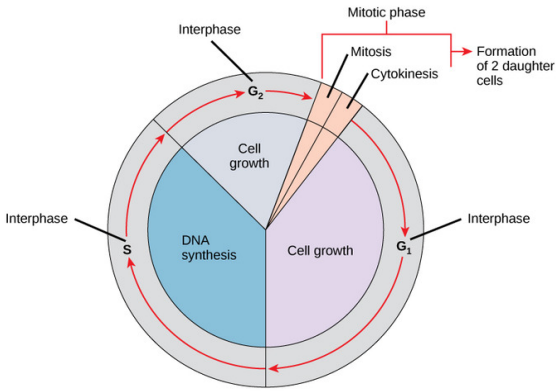

Figure: **The Cell Cycle**: The cell cycle consists of interphase and the mitotic phase. During interphase, the cell grows and the nuclear DNA is duplicated. Interphase is followed by the mitotic phase. During the mitotic phase, the duplicated chromosomes are segregated and distributed into daughter nuclei. The cytoplasm is usually divided as well, resulting in two daughter cells

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7.9B: The Relationship Between Genes and Proteins

Proteins, encoded by individual genes, orchestrate nearly every function of the cell.

LEARNING OBJECTIVES

Describe transcription and translation

Key Takeaways

Key Points

- Genes are composed of DNA arranged on chromosomes.
- Some genes encode structural or regulatory RNAs. Other genes encode proteins.
- Replication copies DNA; transcription uses DNA to make complementary RNAs; translation uses mRNAs to make proteins.
- In eukaryotic cells, replication and transcription take place within the nucleus while translation takes place in the cytoplasm.
- In prokaryotic cells, replication, transcription, and translation occur in the cytoplasm.

Key Terms

- **DNA**: a biopolymer of deoxyribonucleic acids (a type of nucleic acid) that has four different chemical groups, called bases: adenine, guanine, cytosine, and thymine
- **messenger RNA**: Messenger RNA (mRNA) is a molecule of RNA that encodes a chemical "blueprint" for a protein product.
- **protein**: any of numerous large, complex naturally-produced molecules composed of one or more long chains of amino acids, in which the amino acid groups are held together by peptide bonds

Genes and Proteins

Since the rediscovery of Mendel's work in 1900, the definition of the gene has progressed from an abstract unit of heredity to a tangible molecular entity capable of replication, transcription, translation, and mutation. Genes are composed of DNA and are linearly arranged on chromosomes. Some genes encode structural and regulatory RNAs. There is increasing evidence from research that profiles the transcriptome of cells (the complete set all RNA transcripts present in a cell) that these may be the largest classes of RNAs produced by eukaryotic cells, far outnumbering the protein-encoding messenger RNAs (mRNAs), but the 20,000 protein-encoding genes typically found in animal cells, and the 30,o00 protein-encoding genes typically found in plant cells, nonetheless have huge impacts on cellular functioning.

Protein-encoding genes specify the sequences of amino acids, which are the building blocks of proteins. In turn, proteins are responsible for orchestrating nearly every function of the cell. Both protein-encoding genes and the proteins that are their gene products are absolutely essential to life as we know it.

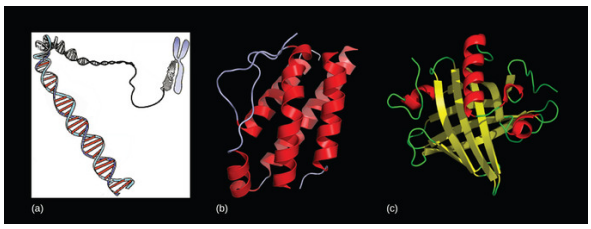

Figure: **Genes Encode Proteins**: Genes, which are carried on (a) chromosomes, are linearly-organized instructions for making the RNA and protein molecules that are necessary for all of processes of life. The (b) interleukin-2 protein and (c) alpha-2u-globulin protein are just two examples of the array of different molecular structures that are encoded by genes.

Replication, Transcription, and Translation are the three main processes used by all cells to maintain their genetic information and to convert the genetic information encoded in DNA into gene products, which are either RNAs or proteins, depending on the gene. In eukaryotic cells, or those cells that have a nucleus, replication and transcription take place within the nucleus while translation takes place outside of the nucleus in cytoplasm. In prokaryotic cells, or those cells that do not have a nucleus, all three processes occur in the cytoplasm.

Replication is the basis for biological inheritance. It copies a cell's DNA. The enzyme DNA polymerase copies a single parental double-stranded DNA molecule into two daughter double-stranded DNA molecules. Transcription makes RNA from DNA. The enzyme RNA polymerase creates an RNA molecule that is complementary to a gene-encoding stretch of DNA. Translation makes

protein from mRNA. The ribosome generates a polypeptide chain of amino acids using mRNA as a template. The polypeptide chain folds up to become a protein.

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SECTION OVERVIEW

7.10: Mutation

Topic hierarchy

7.10A: DNA Repair

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7.10A: DNA Repair

Most mistakes during replication are corrected by DNA polymerase during replication or by post-replication repair mechanisms.

LEARNING OBJECTIVES

Explain how errors during replication are repaired

Key Takeaways

Key Points

- Mismatch repair enzymes recognize mis-incorporated bases, remove them from DNA, and replace them with the correct bases.
- In nucleotide excision repair, enzymes remove incorrect bases with a few surrounding bases, which are replaced with the correct bases with the help of a DNA polymerase and the template DNA.
- When replication mistakes are not corrected, they may result in mutations, which sometimes can have serious consequences.
- Point mutations, one base substituted for another, can be silent (no effect) or may have effects ranging from mild to severe.
- Mutations may also involve insertions (addition of a base), deletion (loss of a base), or translocation (movement of a DNA section to a new location on the same or another chromosome).

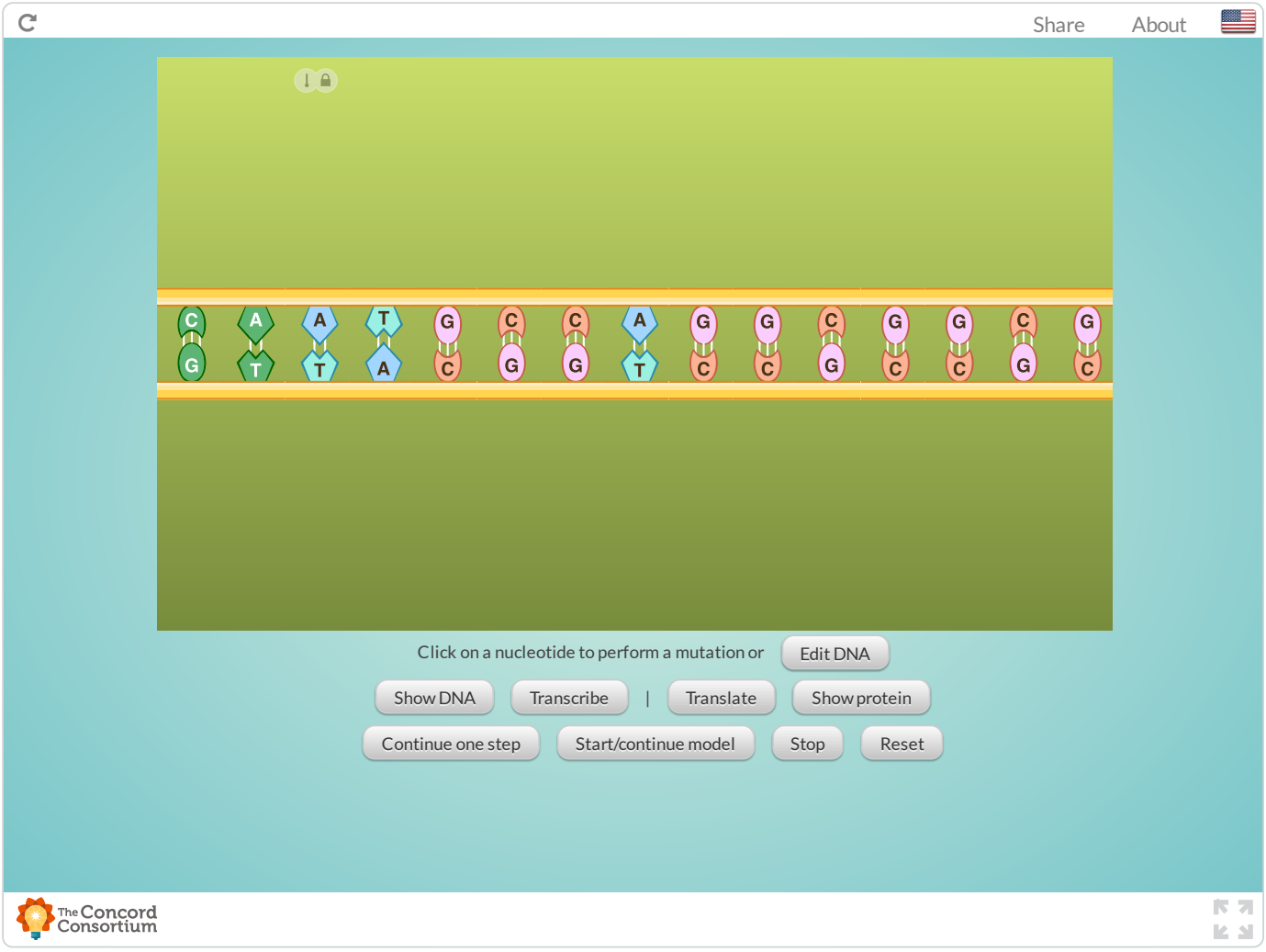
Key Terms

- **mismatch repair**: a system for recognizing and repairing some forms of DNA damage and erroneous insertion, deletion, or mis-incorporation of bases that can arise during DNA replication and recombination
- **nucleotide excision repair**: a DNA repair mechanism that corrects damage done by UV radiation, including thymine dimers and 6,4 photoproducts that cause bulky distortions in the DNA

Errors during Replication

DNA replication is a highly accurate process, but mistakes can occasionally occur as when a DNA polymerase inserts a wrong base. Uncorrected mistakes may sometimes lead to serious consequences, such as cancer. Repair mechanisms can correct the mistakes, but in rare cases mistakes are not corrected, leading to mutations; in other cases, repair enzymes are themselves mutated or defective.

Mutations: In this interactive, you can "edit" a DNA strand and cause a mutation. Take a look at the effects!



Most of the mistakes during DNA replication are promptly corrected by DNA polymerase which proofreads the base that has just been added. In proofreading, the DNA pol reads the newly-added base before adding the next one so a correction can be made. The polymerase checks whether the newly-added base has paired correctly with the base in the template strand. If it is the correct base, the next nucleotide is added. If an incorrect base has been added, the enzyme makes a cut at the phosphodiester bond and releases the incorrect nucleotide. This is performed by the exonuclease action of DNA pol III. Once the incorrect nucleotide has been removed, a new one will be added again.

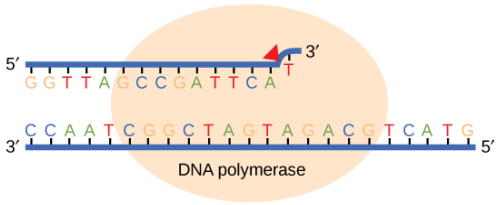


Figure: **DNA polymerase proofreading**: Proofreading by DNA polymerase corrects errors during replication.

Some errors are not corrected during replication, but are instead corrected after replication is completed; this type of repair is known as mismatch repair. The enzymes recognize the incorrectly-added nucleotide and excise it; this is then replaced by the correct base. If this remains uncorrected, it may lead to more permanent damage. How do mismatch repair enzymes recognize which of the two bases is the incorrect one? In *E. coli*, after replication, the nitrogenous base adenine acquires a methyl group; the parental DNA strand will have methyl groups, whereas the newly-synthesized strand lacks them. Thus, DNA polymerase is able to remove the incorrectly-incorporated bases from the newly-synthesized, non-methylated strand. In eukaryotes, the mechanism is not very well understood, but it is believed to involve recognition of unsealed nicks in the new strand, as well as a short-term continuing association of some of the replication proteins with the new daughter strand after replication has been completed.

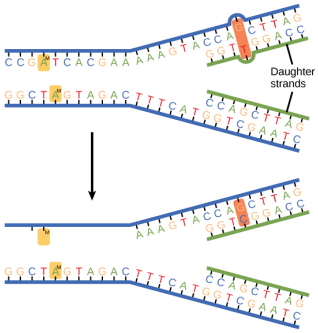


Figure: **Mismatch Repair**: In mismatch repair, the incorrectly-added base is detected after replication. The mismatch-repair proteins detect this base and remove it from the newly-synthesized strand by nuclease action. The gap is now filled with the correctly-paired base.

In another type of repair mechanism, nucleotide excision repair, enzymes replace incorrect bases by making a cut on both the 3′ and 5′ ends of the incorrect base. The segment of DNA is removed and replaced with the correctly-paired nucleotides by the action of DNA pol. Once the bases are filled in, the remaining gap is sealed with a phosphodiester linkage catalyzed by DNA ligase. This repair mechanism is often employed when UV exposure causes the formation of pyrimidine dimers.

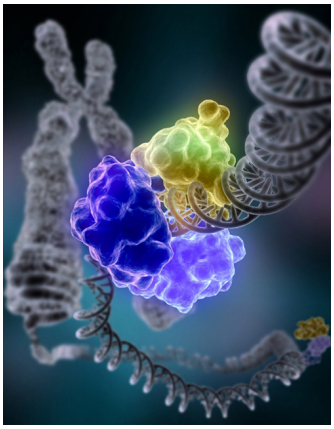


Figure: **DNA Ligase I Repairing Chromosomal Damage**: DNA damage, due to environmental factors and normal metabolic processes inside the cell, occurs at a rate of 1,000 to 1,000,000 molecular lesions per cell per day. A special enzyme, DNA ligase (shown here in color), encircles the double helix to repair a broken strand of DNA. DNA ligase is responsible for repairing the millions of DNA breaks generated during the normal course of a cell's life. Without molecules that can mend such breaks, cells can malfunction, die, or become cancerous. DNA ligases catalyse the crucial step of joining breaks in duplex DNA during DNA repair, replication and recombination, and require either Adenosine triphosphate (ATP) or Nicotinamide adenine dinucleotide (NAD+) as a cofactor.

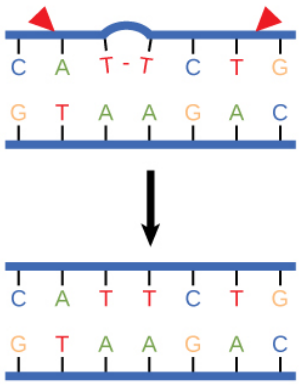


Figure: **Nucleotide Excision Repairs**: Nucleotide excision repairs thymine dimers. When exposed to UV, thymines lying adjacent to each other can form thymine dimers. In normal cells, they are excised and replaced.

DNA Damage and Mutations

Errors during DNA replication are not the only reason why mutations arise in DNA. Mutations, variations in the nucleotide sequence of a genome, can also occur because of damage to DNA. Such mutations may be of two types: induced or spontaneous. Induced mutations are those that result from an exposure to chemicals, UV rays, X-rays, or some other environmental agent. Spontaneous mutations occur without any exposure to any environmental agent; they are a result of natural reactions taking place within the body.

Mutations may have a wide range of effects. Some mutations are not expressed; these are known as silent mutations. Point mutations are those mutations that affect a single base pair. The most common nucleotide mutations are substitutions, in which one base is replaced by another. These can be of two

types: transitions or transversions. Transition substitution refers to a purine or pyrimidine being replaced by a base of the same kind; for example, a purine such as adenine may be replaced by the purine guanine. Transversion substitution refers to a purine being replaced by a pyrimidine or vice versa; for example, cytosine, a pyrimidine, is replaced by adenine, a purine. Mutations can also be the result of the addition of a base, known as an insertion, or the removal of a base, known as a deletion. Sometimes a piece of DNA from one chromosome may get translocated to another chromosome or to another region of the same chromosome.

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SECTION OVERVIEW

7.11: Genetic Transfer in Prokaryotes

Topic hierarchy

7.11A: Generalized Recombination and RecA

7.11B: Bacterial Transformation

7.11C: Bacterial Transduction

7.11D: Prokaryotic Reproduction

7.11E: Complementation

7.11F: Gene Transfer in Archaea

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7.11A: Generalized Recombination and RecA

In homologous recombination, a type of genetic recombination, nucleotide sequences are exchanged between two similar molecules of DNA.

LEARNING OBJECTIVES

Explain the process of homologous recombination in bacteria

Key Takeaways

Key Points

- Homologous recombination can vary among different organisms and cell types, but most forms involve the same basic steps.
- Homologous recombination is a major DNA repair process in bacteria. It is also important for producing genetic diversity in bacterial populations.
- Homologous recombination has been most studied and is best understood for *Escherichia coli*.

Key Terms

- **recombination**: The formation of genetic combinations in offspring that are not present in the parents
- **genetic**: Relating to genetics or genes.
- **homologous**: Showing a degree of correspondence or similarity.

Homologous recombination is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. It is most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks. Homologous recombination also produces new combinations of DNA sequences during meiosis, the process by which eukaryotes make gamete cells, like sperm and egg cells in animals. These new combinations of DNA represent genetic variation in offspring, which in turn enables populations to adapt during the course of evolution. Homologous recombination is also used in horizontal gene transfer to exchange genetic material between different strains and species of bacteria and viruses.

Homologous recombination can vary among different organisms and cell types, but most forms involve the same basic steps. After a double-strand break occurs, sections of DNA around the 5′ ends of the break are cut away in a process called resection. In the strand invasion step that follows, an overhanging 3′ end of the broken DNA molecule then “invades” a similar or identical DNA molecule that is not broken. After strand invasion, one or two cross-shaped structures called Holliday junctions connect the two DNA molecules. Depending on how the two junctions are cut by enzymes, the type of homologous recombination that occurs in meiosis results in either chromosomal crossover or non-crossover. Homologous recombination that occurs during DNA repair tends to result in non-crossover products, in effect restoring the damaged DNA molecule as it existed before the double-strand break.

Homologous recombination is conserved across all three domains of life as well as viruses. Homologous recombination is also used in gene targeting, a technique for introducing genetic changes into target organisms.

Homologous recombination is a major DNA repair process in bacteria. It is also important for producing genetic diversity in bacterial populations. Homologous recombination has been most studied and is best understood for *Escherichia coli*. Double-strand DNA breaks in bacteria are repaired by the RecBCD pathway of homologous recombination. Breaks that occur on one of the two DNA strands, known as single-strand gaps, are thought to be repaired by the RecF pathway. Both the RecBCD and RecF pathways include a series of reactions known as branch migration, in which single DNA strands are exchanged between two intercrossed molecules of duplex DNA, and resolution, in which those two intercrossed molecules of DNA are cut apart and restored to their normal double-stranded state.

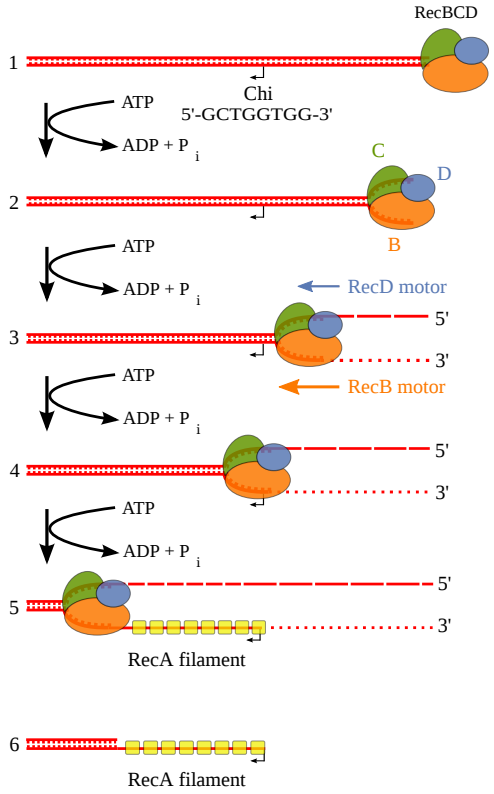

Figure: **Steps in the pre-synapsis phase of homologous recombination in bacteria**: Beginning of the RecBCD pathway. This model is based on reactions of DNA and RecBCD with Mg2+ ions in excess over ATP. Step 1: RecBCD binds to a DNA double strand break. Step 2: RecBCD initiates unwinding of the DNA duplex through ATP-dependent helicase activity. Step 3: RecBCD continues its unwinding and moves down the DNA duplex, cleaving the 3′ strand much more frequently than the 5′ strand. Step 4: RecBCD encounters a Chi sequence and stops digesting the 3′ strand; cleavage of the 5′ strand is significantly increased. Step 5: RecBCD loads RecA onto the 3′ strand. Step 6: RecBCD unbinds from the DNA duplex, leaving a RecA nucleoprotein filament on the 3′ tail.

The RecBCD pathway is the main recombination pathway used in bacteria to repair double-strand breaks in DNA. These double-strand breaks can be caused by UV light and other radiation, as well as chemical mutagens. Double-strand breaks may also arise by DNA replication through a single-strand nick or gap. Such a situation causes what is known as a collapsed replication fork and is fixed by several pathways of homologous recombination including the RecBCD pathway.

In this pathway, a three-subunit enzyme complex called RecBCD initiates recombination by binding to a blunt or nearly blunt end of a break in double-strand DNA. After RecBCD binds the DNA end, the RecB and RecD subunits begin unzipping the DNA duplex through helicase activity. The RecB subunit also has a nuclease domain, which cuts the single strand of DNA that emerges from the unzipping process. This unzipping continues until RecBCD encounters a specific nucleotide sequence (5′-GCTGGTGG-3′) known as a Chi site.

Upon encountering a Chi site, the activity of the RecBCD enzyme changes drastically. DNA unwinding pauses for a few seconds and then resumes at roughly half the initial speed. This is likely because the slower RecB helicase unwinds the DNA after Chi, rather than the faster RecD helicase, which unwinds the DNA before Chi. Recognition of the Chi site also changes the RecBCD enzyme so that it cuts the DNA strand with Chi and begins loading multiple RecA proteins onto the single-stranded DNA with the newly generated 3′ end. The resulting RecA-coated nucleoprotein filament then searches out similar sequences of DNA on a homologous chromosome. The search process induces stretching of the DNA duplex, which enhances homology recognition (a mechanism termed conformational proofreading). Upon finding such a sequence, the single-stranded nucleoprotein filament moves into the homologous recipient DNA duplex in a process called strand invasion. The invading 3′ overhang causes one of the strands of the recipient DNA duplex to be displaced, to form a D-loop. If the D-loop is cut, another swapping of strands forms a cross-shaped structure called a Holliday junction.Resolution of the Holliday junction by some combination of RuvABC or RecG can produce two recombinant DNA molecules with reciprocal genetic types, if the two interacting DNA molecules differ genetically.

Alternatively, the invading 3′ end near Chi can prime DNA synthesis and form a replication fork. This type of resolution produces only one type of recombinant (non-reciprocal).

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7.11B: Bacterial Transformation

Transformation is the direct uptake, incorporation and expression of exogenous genetic material from its surroundings.

LEARNING OBJECTIVES

Differentiate between natural and artificial transformation

Key Takeaways

Key Points

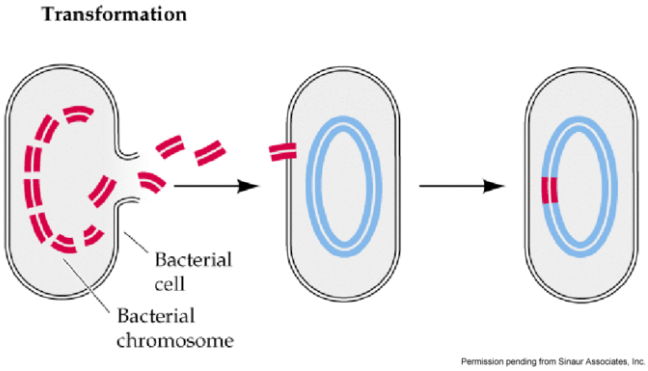
- Transformation results in the genetic alteration of the recipient cell.
- Exogenous DNA is taken up into the recipient cell from its surroundings through the cell membrane (s).
- Transformation occurs naturally in some species of bacteria, but it can also be affected by artificial means in other cells.

Key Terms

- **eukaryotic**: Having complex cells in which the genetic material is organized into membrane-bound nuclei.
- **transformation**: In molecular biology transformation is genetic alteration of a cell resulting from the direct uptake, incorporation and expression of exogenous genetic material (exogenous DNA) from its surroundings and taken up through the cell membrane(s).
- **expression**: Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product.
- **exogenous**: Produced or originating outside of an organism.
- **translocase**: An enzyme that assists in moving another molecule, usually across a membrane.

Genetic Alteration

In molecular biology, transformation is genetic alteration of a cell resulting from the direct uptake, incorporation and expression of exogenous genetic material (exogenous DNA) from its surroundings and taken up through the cell membrane(s).



Transformation: Illustration of bacterial transformation. DNA from dead cells gets cut into fragments and exits the cell. The free-floating DNA can then be picked up by competent cells. The exogenous DNA is incorporated into the host cell's chromosome via recombination.

NATURAL TRANSFORMATION

Transformation occurs naturally in some species of bacteria, but it can also be effected by artificial means in other cells. For transformation to happen, bacteria must be in a state of competence, which might occur as a time-limited response to environmental conditions such as starvation and cell density. Transformation is one of three processes by which exogenous genetic material may be introduced into a bacterial cell; the other two being conjugation (transfer of genetic material between two bacterial cells in direct contact), and transduction (injection of foreign DNA by a bacteriophage virus into the host bacterium).

"*Transformation*" may also be used to describe the insertion of new genetic material into nonbacterial cells, including animal and plant cells; however, because "transformation" has a special meaning in relation to animal cells, indicating progression to a

cancerous state, the term should be avoided for animal cells when describing introduction of exogenous genetic material. Introduction of foreign DNA into eukaryotic cells is often called "*transfection*".

Bacterial transformation may be referred to as a stable genetic change, brought about by the uptake of naked DNA (DNA without associated cells or proteins). Competence refers to the state of being able to take up exogenous DNA from the environment. There are two forms of competence: natural and artificial.

About 1% of bacterial species are capable of naturally taking up DNA under laboratory conditions; more may be able to take it up in their natural environments. DNA material can be transferred between different strains of bacteria in a process that is called horizontal gene transfer.

Some species, upon cell death, release their DNA to be taken up by other cells; however, transformation works best with DNA from closely-related species. These naturally-competent bacteria carry sets of genes that provide the protein machinery to bring DNA across the cell membrane(s). The transport of the exogeneous DNA into the cells may require proteins that are involved in the assembly of type IV pili and type II secretion system, as well as DNA translocase complex at the cytoplasmic membrane.

GRAM-POSITIVE AND GRAM-NEGATIVE DIFFERENCES

Due to the differences in structure of the cell envelope between Gram-positive and Gram-negative bacteria, there are some differences in the mechanisms of DNA uptake in these cells. However, most of them share common features that involve related proteins. The DNA first binds to the surface of the competent cells on a DNA receptor, and passes through the cytoplasmic membrane via DNA translocase. Only single-stranded DNA may pass through, one strand is therefore degraded by nucleases in the process, and the translocated single-stranded DNA may then be integrated into the bacterial chromosomes by a RecA-dependent process.

In Gram-negative cells, due to the presence of an extra membrane, the DNA requires the presence of a channel formed by secretins on the outer membrane. Pilin may be required for competence however, its role is uncertain. The uptake of DNA is generally non-sequence specific, although in some species the presence of specific DNA uptake sequences may facilitate efficient DNA uptake.

ARTIFICIAL TRANSFER

Artificial competence can be induced in laboratory procedures that involve making the cell passively permeable to DNA, by exposing it to conditions that do not normally occur in nature. Typically, the cells are incubated in a solution containing divalent cations; most commonly, calcium chloride solution under cold condition, which is then exposed to a pulse of heat shock. However, the mechanism of the uptake of DNA via chemically-induced competence in this calcium chloride transformation method is unclear.

The surface of bacteria such as E. coli is negatively-charged due to phospholipids and lipopolysaccharides on its cell surface, and the DNA is also negatively-charged. One function of the divalent cation therefore, would be to shield the charges by coordinating the phosphate groups and other negative charges, thereby allowing a DNA molecule to adhere to the cell surface. It is suggested that exposing the cells to divalent cations in cold condition may also change or weaken the cell surface structure of the cells making it more permeable to DNA. The heat-pulse is thought to create a thermal imbalance on either side of the cell membrane, which forces the DNA to enter the cells through either cell pores or the damaged cell wall.

Electroporation is another method of promoting competence. Using this method, the cells are briefly shocked with an electric field of 10-20 kV/cm which is thought to create holes in the cell membrane through which the plasmid DNA may enter. After the electric shock, the holes are rapidly closed by the cell's membrane-repair mechanisms.

O. T. Avery, et al. were first to demonstrate that "rough" colonies of S. pneumoniae could be transformed to "smooth" (capsule producing) colonies by addition of DNA extracts of the former to the latter, thus "transforming" them. (See Lederberg below)

1. Lederberg, Joshua (1994). The Transformation of Genetics by DNA: An Anniversary Celebration of AVERY, MACLEOD and MCCARTY(1944) in Anecdotal, Historical and Critical Commentaries on Genetics. The Rockfeller University, New York, New York 10021-6399. PMID 8150273.

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7.11C: Bacterial Transduction

Transduction is the process by which DNA is transferred from one bacterium to another by a virus.

LEARNING OBJECTIVES

Differentiate between generalized and specialized transduction

Key Takeaways

Key Points

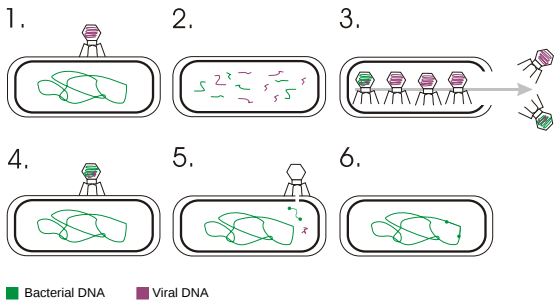
- Transduction does not require physical contact between the cell donating the DNA and the cell receiving the DNA (which occurs in conjugation), and it is DNAase resistant.
- Transduction happens through either the lytic cycle or the lysogenic cycle.
- Transduction is especially important because it explains one mechanism by which antibiotic drugs become ineffective due to the transfer of antibiotic-resistance genes between bacteria.

Key Terms

- **lytic cycle**: The normal process of viral reproduction involving penetration of the cell membrane, nucleic acid synthesis, and lysis of the host cell.
- **lysogenic cycle**: A form of viral reproduction involving the fusion of the nucleic acid of a bacteriophage with that of a host, followed by proliferation of the resulting prophage.
- **transduction**: Transduction is the process by which DNA is transferred from one bacterium to another by a virus.

Transduction

Transduction is the process by which DNA is transferred from one bacterium to another by a virus. It also refers to the process whereby foreign DNA is introduced into another cell via a viral vector. Transduction does not require physical contact between the cell donating the DNA and the cell receiving the DNA (which occurs in conjugation), and it is DNAase resistant (transformation is susceptible to DNAase). Transduction is a common tool used by molecular biologists to stably introduce a foreign gene into a host cell's genome.



Transduction: Transduction is the process by which DNA is transferred from one bacterium to another by a virus. It also refers to the process whereby foreign DNA is introduced into another cell via a viral vector.

When bacteriophages (viruses that infect bacteria) infect a bacterial cell, their normal mode of reproduction is to harness the replicational, transcriptional, and translation machinery of the host bacterial cell to make numerous virions, or complete viral particles, including the viral DNA or RNA and the protein coat.

Transduction is especially important because it explains one mechanism by which antibiotic drugs become ineffective due to the transfer of antibiotic-resistance genes between bacteria. In addition, hopes to create medical methods of genetic modification of diseases such as Duchenne/Becker Muscular Dystrophy are based on these methodologies.

The Lytic Cycle and the Lysogenic Cycle

Transduction happens through either the lytic cycle or the lysogenic cycle. If the lysogenic cycle is adopted, the phage chromosome is integrated (by covalent bonds) into the bacterial chromosome, where it can remain dormant for thousands of generations. If the

lysogen is induced (by UV light for example), the phage genome is excised from the bacterial chromosome and initiates the lytic cycle, which culminates in lysis of the cell and the release of phage particles. The lytic cycle leads to the production of new phage particles which are released by lysis of the host.

Transduction is a method for transferring genetic material. The packaging of bacteriophage DNA has low fidelity and small pieces of bacterial DNA, together with the bacteriophage genome, may become packaged into the bacteriophage genome. At the same time, some phage genes are left behind in the bacterial chromosome.

There are generally three types of recombination events that can lead to this incorporation of bacterial DNA into the viral DNA, leading to two modes of recombination.

Generalized transduction is the process by which any bacterial gene may be transferred to another bacterium via a bacteriophage, and typically carries only bacterial DNA and no viral DNA. In essence, this is the packaging of bacterial DNA into a viral envelope. This may occur in two main ways, recombination and headful packaging.

If bacteriophages undertake the lytic cycle of infection upon entering a bacterium, the virus will take control of the cell's machinery for use in replicating its own viral DNA. If by chance bacterial chromosomal DNA is inserted into the viral capsid which is usually used to encapsulate the viral DNA, the mistake will lead to generalized transduction.

If the virus replicates using "headful packaging," it attempts to fill the nucleocapsid with genetic material. If the viral genome results in spare capacity, viral packaging mechanisms may incorporate bacterial genetic material into the new virion.

The new virus capsule, now loaded with part bacterial DNA, continues to infect another bacterial cell. This bacterial material may become recombined into another bacterium upon infection.

Fates of DNA Inserted into the Recipient Cell

When the new DNA is inserted into this recipient cell it can fall to one of three fates: the DNA will be absorbed by the cell and be recycled for spare parts; if the DNA was originally a plasmid, it will recirculate inside the new cell and become a plasmid again; if the new DNA matches with a homologous region of the recipient cell's chromosome, it will exchange DNA material similar to the actions in conjugation. This type of recombination is random and the amount recombined depends on the size of the virus being used.

Specialized transduction is the process by which a restricted set of bacterial genes are transferred to another bacterium. The genes that get transferred (donor genes) depend on where the phage genome is located on the chromosome. Specialized transduction occurs when the prophage excises imprecisely from the chromosome so that bacterial genes lying adjacent to the prophage are included in the excised DNA. The excised DNA is then packaged into a new virus particle, which can then deliver the DNA to a new bacterium, where the donor genes can be inserted into the recipient chromosome or remain in the cytoplasm, depending on the nature of the bacteriophage.

When the partially encapsulated phage material infects another cell and becomes a "prophage" (is covalently bonded into the infected cell's chromosome), the partially coded prophage DNA is called a "heterogenote. " Example of specialized transduction is λ phages in *Escherichia coli*, which was discovered by Esther Lederberg.

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7.11D: Prokaryotic Reproduction

Prokaryotes reproduce asexually by binary fission; they can also exchange genetic material by transformation, transduction, and conjugation.

LEARNING OBJECTIVES

Distinguish among the types of reproduction in prokaryotes

Key Takeaways

Key Points

- Binary fission is a type of reproduction in which the chromosome is replicated and the resultant prokaryote is an exact copy of the parental prokaryate, thus leaving no opportunity for genetic diversity.
- Transformation is a type of prokaryotic reproduction in which a prokaryote can take up DNA found within the environment that has originated from other prokaryotes.
- Transduction is a type of prokaryotic reproduction in which a prokaryote is infected by a virus which injects short pieces of chromosomal DNA from one bacterium to another.
- Conjugation is a type of prokaryotic reproduction in which DNA is transferred between prokaryotes by means of a pilus.

Key Terms

- **transformation**: the alteration of a bacterial cell caused by the transfer of DNA from another, especially if pathogenic
- **transduction**: horizontal gene transfer mechanism in prokaryotes where genes are transferred using a virus
- **binary fission**: the process whereby a cell divides asexually to produce two daughter cells
- **conjugation**: the temporary fusion of organisms, especially as part of sexual reproduction
- **pilus**: a hairlike appendage found on the cell surface of many bacteria

Reproduction

Reproduction in prokaryotes is asexual and usually takes place by binary fission. The DNA of a prokaryote exists as as a single, circular chromosome. Prokaryotes do not undergo mitosis; rather the chromosome is replicated and the two resulting copies separate from one another, due to the growth of the cell. The prokaryote, now enlarged, is pinched inward at its equator and the two resulting cells, which are clones, separate. Binary fission does not provide an opportunity for genetic recombination or genetic diversity, but prokaryotes can share genes by three other mechanisms.

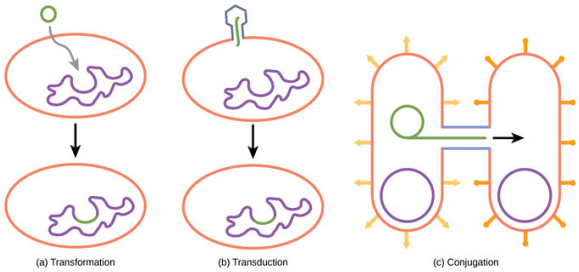

Figure: **Modes of prokaryote reproduction**: Besides binary fission, there are three other mechanisms by which prokaryotes can exchange DNA. In (a) transformation, the cell takes up prokaryotic DNA directly from the environment. The DNA may remain separate as plasmid DNA or be incorporated into the host genome. In (b) transduction, a bacteriophage injects DNA into the cell that contains a small fragment of DNA from a different prokaryote. In (c) conjugation, DNA is transferred from one cell to another via a mating bridge that connects the two cells after the pilus draws the two bacteria close enough to form the bridge.

In transformation, the prokaryote takes in DNA found in its environment that is shed by other prokaryotes. If a nonpathogenic bacterium takes up DNA for a toxin gene from a pathogen and incorporates the new DNA into its own chromosome, it, too, may become pathogenic. In transduction, bacteriophages, the viruses that infect bacteria, sometimes also move short pieces of chromosomal DNA from one bacterium to another. Transduction results in a recombinant organism. Archaea are not affected by bacteriophages, but instead have their own viruses that translocate genetic material from one individual to another. In conjugation, DNA is transferred from one prokaryote to another by means of a pilus, which brings the organisms into contact with one another. The DNA transferred can be in the form of a plasmid or as a hybrid, containing both plasmid and chromosomal DNA.

Reproduction can be very rapid: a few minutes for some species. This short generation time, coupled with mechanisms of genetic recombination and high rates of mutation, result in the rapid evolution of prokaryotes, allowing them to respond to environmental changes (such as the introduction of an antibiotic) very rapidly.

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7.11E: Complementation

Learning Objectives

- Explain the mechanism of genetic complementation

Complementation refers to a relationship between two different strains of an organism which both have homozygous recessive mutations that produce the same phenotype (for example, a change in wing structure in flies) but which do not reside on the same (homologous) gene.

These strains are true breeding for their mutation. If, when these strains are crossed with each other, some offspring show recovery of the wild-type phenotype, they are said to show "genetic complementation". When this occurs, each strain's haploid supplies a wild-type allele to "complement" the mutated allele of the other strain's haploid, causing the offspring to have heterozygous mutations in all related genes. Since the mutations are recessive, the offspring will display the wild-type phenotype.

A complementation test (sometimes called a "cis-trans" test) refers to this experiment, developed by American geneticist Edward B. Lewis. It answers the question: "Does a wild-type copy of gene X rescue the function of the mutant allele that is believed to define gene X?". If there is an allele with an observable phenotype whose function can be provided by a wild type genotype (i.e., the allele is recessive), one can ask whether the function that was lost because of the recessive allele can be provided by another mutant genotype. If not, the two alleles must be defective in the same gene. The beauty of this test is that the trait can serve as a read-out of gene function even without knowledge of what the gene is doing at a molecular level.

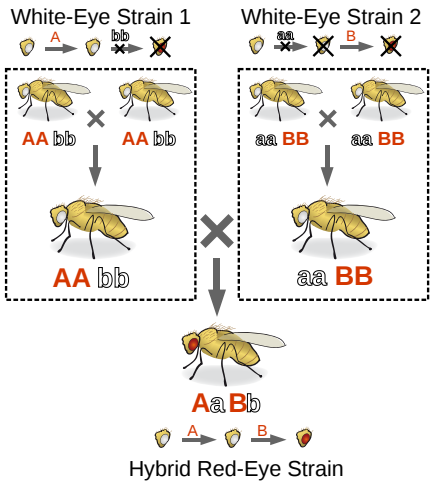

Figure: ***Complementation Test****: Example of a complementation test. Two strains of flies are white eyed because of two different autosomal recessive mutations which interrupt different steps in a single pigment-producing metabolic pathway. Flies from Strain 1 have complementary mutations to flies from Strain 2 because when they are crossed the offspring are able to complete the full metabolic pathway and thus have red eyes.*

Complementation arises because loss of function in genes responsible for different steps in the same metabolic pathway can give rise to the same phenotype. When strains are bred together, offspring inherit wildtype versions of each gene from either parent. Because the mutations are recessive, there is a recovery of function in that pathway, so offspring recover the wild-type phenotype. Thus, the test is used to decide if two independently derived recessive mutant phenotypes are caused by mutations in the same gene or in two different genes. If both parent strains have mutations in the same gene, no normal versions of the gene are inherited by the offspring; they express the same mutant phenotype and complementation has failed to occur.

In other words, if the combination of two haploid genomes containing different recessive mutations yields a mutant phenotype, then there are three possibilities: Mutations occur in the same gene; One mutation affects the expression of the other; One mutation may result in an inhibitory product. If the combination of two haploid genomes containing different recessive mutations yields the wild type phenotype, then the mutations must be in different genes.

Key Points

- A complementation test answers the question: “Does a wild-type copy of gene X rescue the function of the mutant allele that is believed to define gene X? “.
- Complementation arises because loss of function in genes responsible for different steps in the same metabolic pathway can give rise to the same phenotype.
- When strains are bred together, offspring inherit wildtype versions of each gene from either parent.

Key Terms

- **Complementation**: In genetics, complementation refers to a relationship between two different strains of an organism which both have homozygous recessive mutations that produce the same phenotype (for example, a change in wing structure in flies) but which do not reside on the same (homologous) gene.
- **mutation**: Any heritable change of the base-pair sequence of genetic material.
- **homozygous**: of an organism in which both copies of a given gene have the same allele

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7.11F: Gene Transfer in Archaea

Archaea are distinct from bacteria and eukaryotes, but genetic material can be transferred between them and between Archaea themselves.

LEARNING OBJECTIVES

Describe the mechanisms of gene transfer in Archaea

Key Takeaways

Key Points

- Archaea while being very different from eukaryotes and bacteria, there are many commonalities at the the genetic level between them.
- Horizontal gene transfer can explain the similarities between the genes found in the three domains of life and indeed there is evidence that horizontal gene transfer occurs with Archaea species.
- Archaea can be infected by double-stranded DNA viruses, which can account for gene transfers, as well like bacteria, Archaea may conjugate.

Key Terms

- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei that are fundamentally from bacteria.
- **translation**: Translation is the communication of the meaning of a source-language text by means of an equivalent target-language text.
- **transcription**: Transcription is the process of creating a complementary RNA copy of a sequence of DNA. Both RNA and DNA are nucleic acids, which use base pairs of nucleotides as a complementary language that can be converted back and forth from DNA to RNA by the action of the correct enzymes.

Archaea are genetically distinct from bacteria and eukaryotes, but are poorly understood: many of the genes that Archaea encode are of unknown function. Transcription and translation in archaea resemble the same processes more closely in eukaryotes than in bacteria, with the archaean RNA polymerase and ribosomes being very close to their equivalents in eukaryotes.

Although Archaea only have one type of RNA polymerase, its structure and function in transcription is similar to that of the eukaryotic RNA polymerase II, with similar protein assemblies (the general transcription factors) directing the binding of the RNA polymerase to a gene's promoter. However, other archaean transcription factors are closer to those found in bacteria. Post-transcriptional modification is simpler than in eukaryotes, since most archaean genes lack introns, although there are many introns in their transfer RNA and ribosomal RNA genes, and introns may occur in a few protein-encoding genes. This is all to say there are many similarities in the genes shared between Archaea and the other domains of life, suggesting there was a transfer of genetic material between the domains of life. This phenomenon is described as horizontal gene transfer.

Horizontal gene transfer (HGT) refers to the transfer of genes between organisms in a manner other than traditional reproduction. Also termed lateral gene transfer, it contrasts with vertical transfer, the transmission of genes from the parental generation to offspring via sexual or asexual reproduction. HGT has been shown to be an important factor in the evolution of many organisms, including bacteria, plants and humans.

Archaea show high levels of horizontal gene transfer between lineages. Some researchers suggest that individuals can be grouped into species-like populations given highly similar genomes and infrequent gene transfer to/from cells with less-related genomes, as in the Archaea genus Ferroplasma. On the other hand, studies in Halorubrum found significant genetic transfer to/from less-related populations. These gene transfers are identified by sequencing the DNA of various Archaea species; through the similarities and differences of the DNA of the different types of Archaea it is determined if the gene was perfectly transferred or from a common ancestor. The elucidation of this can be controversial.

How genetic material can move from one Archaea to another is poorly understood. In bacteria the natural ways in which this occurs is through either bacterial conjugation or viral transfer, also known as transduction. Conjugation is where two (sometimes distantly related) bacteria transfer genetic material by direct contact. Transduction occurs when a virus "picks up" some DNA from its host and when infecting a new host, moves that genetic material to the new host. It is thought that conjugation can occur in Archaea, though unlike bacteria the mechanism is not well understood. As well Archaea can be infected by viruses. In fact Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes,

including bottles, hooked rods, or teardrops. Taken together it is clear that gene transfer happens in Archaea, and probably is similar to horizontal gene transfer seen in the other domains of life.

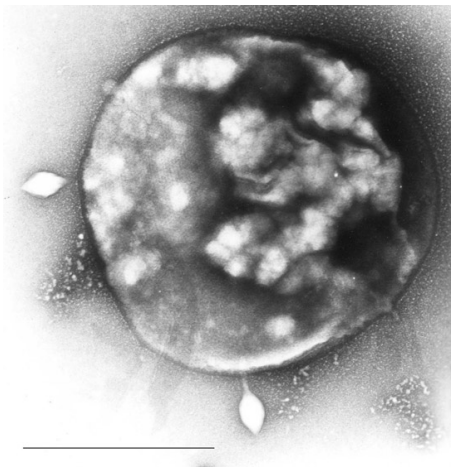

Figure: **Archaeal viral infection**: Cell of Sulfolobus infected by virus STSV1 observed under microscopy. Two spindle-shaped viruses were being released from the host cell. The strain of Sulfolobus and STSV1 (Sulfolobus tengchongensis Spindle-shaped Virus 1) were isolated by Xiaoyu Xiang and his colleagues in an acidic hot spring in Yunnan Province, China. At present, STSV1 is the largest archaeal virus to have been isolated and studied. Its genome sequence has been sequenced.

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SECTION OVERVIEW

7.12: Tools of Genetic Engineering

Topic hierarchy

7.12A: Recombinant DNA Technology

7.12B: Selection

7.12C: Mutation

7.12D: Reproductive Cloning

7.12E: Basic Techniques to Manipulate Genetic Material (DNA and RNA)

7.12F: Molecular and Cellular Cloning

7.12G: Plasmids as Cloning Vectors

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7.12A: Recombinant DNA Technology

Molecular cloning permits the replication of a specific DNA sequence in a living microorganism.

LEARNING OBJECTIVES

Show some of the methods and uses of recombinant DNA

Key Takeaways

Key Points

- Although a very large number of host organisms and molecular cloning vectors are in use, the great majority of molecular cloning experiments begin with a laboratory strain of the bacterium *E. coli* (*Escherichia coli*) and a plasmid cloning vector.
- *E. coli* and plasmid vectors are in common use because they are technically sophisticated, versatile, widely available, and offer rapid growth of recombinant organisms with minimal equipment.
- Modern bacterial cloning vectors (e.g. pUC19) use the blue-white screening system to distinguish colonies (clones) of transgenic cells from those that contain the parental vector.

Key Terms

- **polymerase chain reaction**: A technique in molecular biology for creating multiple copies of DNA from a sample; used in genetic fingerprinting etc.
- **molecular cloning**: a set of experimental methods in molecular biology that are used to assemble recombinant DNA molecules and to direct their replication within host organisms.
- **restriction enzyme**: An endonuclease that catalyzes double-strand cleavage of DNA containing a specific sequence.

Recombinant DNA technology also referred to as molecular cloning is similar to polymerase chain reaction (PCR) in that it permits the replication of a specific DNA sequence. The fundamental difference between the two methods is that molecular cloning involves replication of the DNA in a living microorganism, while PCR replicates DNA in an *in vitro* solution, free of living cells.

In standard molecular cloning experiments, the cloning of any DNA fragment essentially involves seven steps:

1. Choice of host organism and cloning vector
2. Preparation of vector DNA
3. Preparation of DNA to be cloned
4. Creation of recombinant DNA
5. Introduction of recombinant DNA into host organism
6. Selection of organisms containing recombinant DNA
7. Screening for clones with desired DNA inserts and biological properties

Although a very large number of host organisms and molecular cloning vectors are in use, the great majority of molecular cloning experiments begin with a laboratory strain of the bacterium *E. coli* (*Escherichia coli*) and a plasmid cloning vector. *E. coli* and plasmid vectors are in common use because they are technically sophisticated, versatile, widely available, and offer rapid growth of recombinant organisms with minimal equipment. The cloning vector is treated with a restriction endonuclease to cleave the DNA at the site where foreign DNA will be inserted. The restriction enzyme is chosen to generate a configuration at the cleavage site that is compatible with that at the ends of the foreign DNA.

Typically, this is done by cleaving the vector DNA and foreign DNA with the same restriction enzyme, for example *EcoRI*. Most modern vectors contain a variety of convenient cleavage sites that are unique within the vector molecule (so that the vector can only be cleaved at a single site) and is located within a gene (frequently beta-galactosidase) whose inactivation can be used to distinguish recombinant from non-recombinant organisms at a later step in the process. To improve the ratio of recombinant to non-recombinant organisms, the cleaved vector may be treated with an enzyme (alkaline phosphatase) that dephosphorylates the vector ends. Vector molecules with dephosphorylated ends are unable to replicate, and replication can only be restored if foreign DNA is integrated into the cleavage site.

For cloning of genomic DNA, the DNA to be cloned is extracted from the organism of interest. Polymerase chain reaction (PCR) methods are often used for amplification of specific DNA or RNA (RT-PCR) sequences prior to molecular cloning. The purified DNA is then treated with a restriction enzyme to generate fragments with ends capable of being linked to those of the vector. If

necessary, short double-stranded segments of DNA (linkers) containing desired restriction sites may be added to create end structures that are compatible with the vector. The creation of recombinant DNA is in many ways the simplest step of the molecular cloning process. DNA prepared from the vector and foreign source are simply mixed together at appropriate concentrations and exposed to an enzyme (DNA ligase) that covalently links the ends together. This joining reaction is often termed ligation. The resulting DNA mixture containing randomly joined ends is then ready for introduction into the host organism. The DNA mixture, previously manipulated *in vitro*, is moved back into a living cell, referred to as the host organism. The methods used to get DNA into cells are varied, and the name applied to this step in the molecular cloning process will often depend upon the experimental method that is chosen (e.g. transformation, transduction, transfection, electroporation).

When microorganisms are able to take up and replicate DNA from their local environment, the process is termed transformation, and cells that are in a physiological state such that they can take up DNA are said to be competent. When bacterial cells are used as host organisms, the selectable marker is usually a gene that confers resistance to an antibiotic that would otherwise kill the cells, typically ampicillin. Cells harboring the vector will survive when exposed to the antibiotic, while those that have failed to take up vector sequences will die. Modern bacterial cloning vectors (e.g. pUC19) use the blue-white screening system to distinguish colonies (clones) of transgenic cells from those that contain the parental vector.

In these vectors, foreign DNA is inserted into a sequence that encodes an essential part of beta-galactosidase, an enzyme whose activity results in formation of a blue-colored colony on the culture medium that is used for this work. Insertion of the foreign DNA into the beta-galactosidase coding sequence disables the function of the enzyme, so that colonies containing recombinant plasmids remain colorless (white). Therefore, recombinant clones are easily identified.

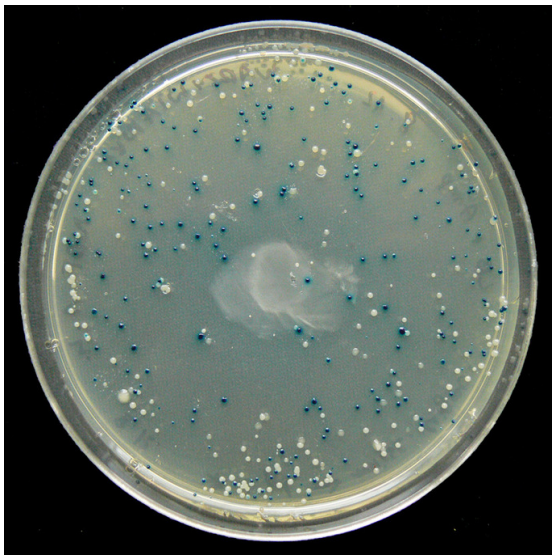

Figure: **Blue White screen**: The blue-white screen is a screening technique that allows for the detection of successful ligations in vector-based gene cloning. DNA of interest is ligated into a vector. The vector is then transformed into competent cell (bacteria). The competent cells are grown in the presence of X-gal. If the ligation was successful, the bacterial colony will be white; if not, the colony will be blue. This technique allows for the quick and easy detection of successful ligation.

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7.12B: Selection

A selectable marker is usually a gene that confers resistance to an antibiotic that would otherwise kill the cells.

LEARNING OBJECTIVES

Identify the purpose of selection in genetic engineering

Key Takeaways

Key Points

- Recombinant DNA is introduced into the organism from which the replication sequences were obtained, then the foreign DNA will be replicated along with the host cell's DNA in the transgenic organism.
- Artificial genetic selection is the process in which cells that have not taken up DNA are selectively killed, and only those cells that can actively replicate DNA containing the selectable marker gene encoded by the vector are able to survive.
- When bacterial cells are used as host organisms, the selectable marker is usually a gene that confers resistance to an antibiotic that would otherwise kill the cells, typically ampicillin.

Key Terms

- **molecular cloning**: a set of experimental methods in molecular biology that are used to assemble recombinant DNA molecules and to direct their replication within host organisms.
- **PCR**: polymerase chain reaction

Scientists who do experimental genetics employ artificial selection experiments that permit the survival of organisms with user-defined phenotypes. Artificial selection is widely used in the field of microbial genetics, especially molecular cloning.

DNA recombination has been used to create gene replacements, deletions, insertions, inversions. Gene cloning and gene/protein tagging is also common. For gene replacements or deletions, usually a cassette encoding a drug-resistance gene is made by PCR.

Molecular cloning is a set of experimental methods in molecular biology that are used to assemble recombinant DNA molecules and to direct their replication within host organisms. The use of the word cloning refers to the fact that the method involves the replication of a single DNA molecule starting from a single living cell to generate a large population of cells containing identical DNA molecules. Molecular cloning generally uses DNA sequences from two different organisms: the species that is the source of the DNA to be cloned, and the species that will serve as the living host for replication of the recombinant DNA. Molecular cloning methods are central to many contemporary areas of modern biology and medicine.

In a conventional molecular cloning experiment, the DNA to be cloned is obtained from an organism of interest. It is then treated with enzymes in the test tube to generate smaller DNA fragments. Subsequently, these fragments are then combined with vector DNA to generate recombinant DNA molecules. The recombinant DNA is then introduced into a host organism (typically an easy-to-grow, benign, laboratory strain of *E. coli* bacteria). This will generate a population of organisms in which recombinant DNA molecules are replicated along with the host DNA. Because they contain foreign DNA fragments, these are transgenic or genetically-modified microorganisms (GMO). This process takes advantage of the fact that a single bacterial cell can be induced to take up and replicate a single recombinant DNA molecule. This single cell can then be expanded exponentially to generate a large amount of bacteria, each of which contain copies of the original recombinant molecule. Thus, both the resulting bacterial population, and the recombinant DNA molecule, are commonly referred to as "clones". Strictly speaking, recombinant DNA refers to DNA molecules, while molecular cloning refers to the experimental methods used to assemble them.

Molecular cloning takes advantage of the fact that the chemical structure of DNA is fundamentally the same in all living organisms. Therefore, if any segment of DNA from any organism is inserted into a DNA segment containing the molecular sequences required for DNA replication, and the resulting recombinant DNA is introduced into the organism from which the replication sequences were obtained, then the foreign DNA will be replicated along with the host cell's DNA in the transgenic organism.

Molecular cloning is similar to polymerase chain reaction (PCR) in that it permits the replication of a specific DNA sequence. The fundamental difference between the two methods is that molecular cloning involves replication of the DNA in a living microorganism, while PCR replicates DNA in an in vitro solution, free of living cells. Whichever method is used, the introduction of recombinant DNA into the chosen host organism is usually a low efficiency process; that is, only a small fraction of the cells

will actually take up DNA. Experimental scientists deal with this issue through a step of artificial genetic selection, in which cells that have not taken up DNA are selectively killed, and only those cells that can actively replicate DNA containing the selectable marker gene encoded by the vector are able to survive. When bacterial cells are used as host organisms, the selectable marker is usually a gene that confers resistance to an antibiotic that would otherwise kill the cells, typically ampicillin. Cells harboring the vector will survive when exposed to the antibiotic, while those that fail to take up vector sequences die. When mammalian cells (e.g. human or mouse cells) are used, a similar strategy is used, except that the marker gene (in this case typically encoded as part of the kanMX cassette) confers resistance to the antibiotic Geneticin.

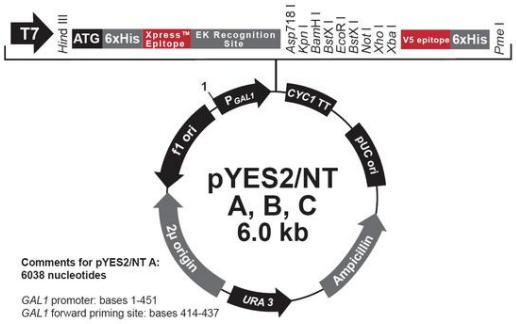

Figure: **Plasmid vector map**: This vector confers amplicillin resistance.

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7.12C: Mutation

Mutations are accidental changes in a genomic sequence of DNA; this includes the DNA sequence of a cell's genome or the DNA or RNA sequence.

LEARNING OBJECTIVES

Explain genetic manipulation through mutations

Key Takeaways

Key Points

- Mutations are caused by radiation, viruses, transposons, and mutagenic chemicals. They are also caused by errors that occur during meiosis or DNA replication.
- Site-directed mutagenesis, also called site-specific mutagenesis or oligonucleotide-directed mutagenesis, is a molecular biology technique often used in biomolecular engineering in which a mutation is created at a defined site in a DNA molecule.
- The basic procedure requires the synthesis of a short DNA primer. This synthetic primer contains the desired mutation. It is complementary to the template DNA around the mutation site so it can hybridize with the DNA in the gene of interest.

Key Terms

- **site-directed mutagenesis**: Also called site-specific mutagenesis or oligonucleotide-directed mutagenesis, is a molecular biology technique often used in biomolecular engineering in which a mutation is created at a defined site in a DNA molecule.
- **mutation**: Any heritable change of the base-pair sequence of genetic material.

In molecular biology and genetics, mutations are accidental changes in a genomic sequence of DNA: the DNA sequence of a cell's genome or the DNA or RNA sequence in some viruses. These random sequences can be defined as sudden and spontaneous changes in the cell. Mutations are caused by radiation, viruses, transposons, and mutagenic chemicals. They are also caused by errors that occur during meiosis or DNA replication. They can also be induced by the organism itself, through cellular processes such as hypermutation.

Site-directed mutagenesis, also called site-specific mutagenesis or oligonucleotide-directed mutagenesis, is a molecular biology technique often used in biomolecular engineering in which a mutation is created at a defined site in a DNA molecule. In general, this form of mutagenesis requires that the wild type gene sequence be known. It is commonly used in protein engineering.

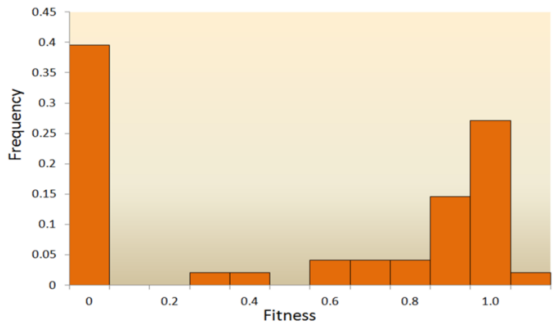

Figure: **The distribution of fitness effects**: The distribution of fitness effects of mutations in vesicular stomatitis virus. In this experiment, random mutations were introduced into the virus by site-directed mutagenesis. The fitness of each mutant was compared with the ancestral type. A fitness of zero, less than one, one, more than one, respectively, indicates that mutations are lethal, deleterious, neutral, and advantageous.

The basic procedure requires the synthesis of a short DNA primer. This synthetic primer contains the desired mutation and is complementary to the template DNA around the mutation site so it can hybridize with the DNA in the gene of interest. The mutation may be a single base change (a point mutation), multiple base changes, deletion, or insertion. The single-stranded primer is then extended using a DNA polymerase, which copies the rest of the gene. The copied gene contains the mutated site. It is then introduced into a host cell as a vector and cloned. Finally, mutants are selected.

The original method using single-primer extension was inefficient due to a lower yield of mutants. The resulting mixture may contain both the original unmutated template as well as the mutant strand, producing a mix population of mutant and non-mutant

progenies. The mutants may also be counter-selected due to presence of a mismatch repair system which favors the methylated template DNA. Many approaches have since been developed to improve the efficiency of mutagenesis.

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7.12D: Reproductive Cloning

Reproductive cloning, possible through artificially-induced asexual reproduction, is a method used to make a clone of an entire organism.

LEARNING OBJECTIVES

Differentiate reproductive cloning from cellular and molecular cloning

Key Takeaways

Key Points

- A form of asexual reproduction, parthenogenesis, occurs when an embryo grows and develops without the fertilization of the egg.
- In reproductive cloning, if the haploid nucleus of an egg cell is replaced with a diploid nucleus from the cell of an individual of the same species, it will become a zygote that is genetically identical to the donor.
- Reproductive cloning has become successful, but still has limitations as cloned individuals often exhibit facial, limb, and cardiac abnormalities.
- Therapeutic cloning, the cloning of human embryos as a source of embryonic stem cells, has been attempted in order to produce cells that can be used to treat detrimental diseases or defects.

Key Terms

- **clone**: a living organism produced asexually from a single ancestor, to which it is genetically identical
- **stem cell**: a primal undifferentiated cell from which a variety of other cells can develop through the process of cellular differentiation
- **parthenogenesis**: a form of asexual reproduction where growth and development of embryos occur without fertilization

Reproductive Cloning

Reproductive cloning is a method used to make a clone or an identical copy of an entire multicellular organism. Most multicellular organisms undergo reproduction by sexual means, which involves genetic hybridization of two individuals (parents), making it impossible to generate an identical copy or clone of either parent. Recent advances in biotechnology have made it possible to artificially induce asexual reproduction of mammals in the laboratory.

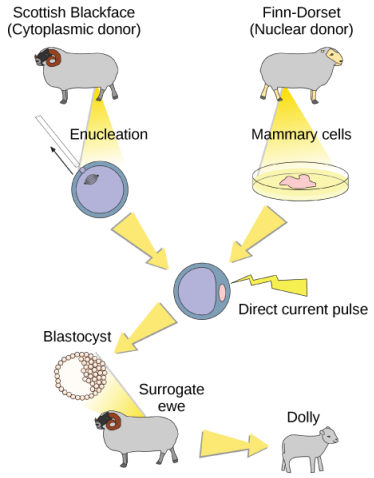

Figure: **Reproductive Cloning of Dolly, the Sheep**: Dolly the sheep was the first mammal to be cloned. To create Dolly, the nucleus was removed from a donor egg cell. The nucleus from a second sheep was then introduced into the cell, which was allowed to divide to the blastocyst stage before being implanted in a surrogate mother.

Parthenogenesis, or “virgin birth,” occurs when an embryo grows and develops without the fertilization of the egg occurring; this is a form of asexual reproduction. An example of parthenogenesis occurs in species in which the female lays an egg. If the egg is fertilized, it is a diploid egg and the individual develops into a female; if the egg is not fertilized, it remains a haploid egg and

develops into a male. The unfertilized egg is called a parthenogenic, or virgin, egg. Some insects and reptiles lay parthenogenic eggs that can develop into adults.

Sexual reproduction requires two cells; when the haploid egg and sperm cells fuse, a diploid zygote results. The zygote nucleus contains the genetic information to produce a new individual. However, early embryonic development requires the cytoplasmic material contained in the egg cell. This idea forms the basis for reproductive cloning. If the haploid nucleus of an egg cell is replaced with a diploid nucleus from the cell of any individual of the same species (called a donor), it will become a zygote that is genetically identical to the donor. Somatic cell nuclear transfer is the technique of transferring a diploid nucleus into an enucleated egg. It can be used for either therapeutic cloning or reproductive cloning.

The first cloned animal was Dolly, a sheep who was born in 1996. The success rate of reproductive cloning at the time was very low. Dolly lived for seven years and died of respiratory complications. There is speculation that because the cell DNA belongs to an older individual, the age of the DNA may affect the life expectancy of a cloned individual. Since Dolly, several animals (e.g. horses, bulls, and goats) have been successfully cloned, although these individuals often exhibit facial, limb, and cardiac abnormalities. There have been attempts at producing cloned human embryos as sources of embryonic stem cells. Sometimes referred to as cloning for therapeutic purposes, the technique produces stem cells that attempt to remedy detrimental diseases or defects (unlike reproductive cloning, which aims to reproduce an organism). Still, therapeutic cloning efforts have met with resistance because of bioethical considerations.

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7.12E: Basic Techniques to Manipulate Genetic Material (DNA and RNA)

Basic techniques used in genetic material manipulation include extraction, gel electrophoresis, PCR, and blotting methods.

LEARNING OBJECTIVES

Distinguish among the basic techniques used to manipulate DNA and RNA

Key Takeaways

Key Points

- The first step to study or work with nucleic acids includes the isolation or extraction of DNA or RNA from cells.
- Gel electrophoresis depends on the negatively-charged ions present on nucleic acids at neutral or basic pH to separate molecules on the basis of size.
- Specific regions of DNA can be amplified through the use of polymerase chain reaction for further analysis.
- Southern blotting involves the transfer of DNA to a nylon membrane, while northern blotting is the transfer of RNA to a nylon membrane; these techniques allow samples to be probed for the presence of certain sequences.

Key Terms

- **denaturation**: the change of folding structure of a protein (and thus of physical properties) caused by heating, changes in pH, or exposure to certain chemicals
- **electrophoresis**: a method for the separation and analysis of large molecules, such as proteins or nucleic acids, by migrating a colloidal solution of them through a gel under the influence of an electric field
- **polymerase chain reaction**: a technique in molecular biology for creating multiple copies of DNA from a sample

Basic Techniques to Manipulate Genetic Material (DNA and RNA)

To understand the basic techniques used to work with nucleic acids, remember that nucleic acids are macromolecules made of nucleotides (a sugar, a phosphate, and a nitrogenous base) linked by phosphodiester bonds. The phosphate groups on these molecules each have a net negative charge. An entire set of DNA molecules in the nucleus is called the genome. DNA has two complementary strands linked by hydrogen bonds between the paired bases. The two strands can be separated by exposure to high temperatures (DNA denaturation) and can be reannealed by cooling. The DNA can be replicated by the DNA polymerase enzyme. Unlike DNA, which is located in the nucleus of eukaryotic cells, RNA molecules leave the nucleus. The most common type of RNA that is analyzed is the messenger RNA (mRNA) because it represents the protein -coding genes that are actively expressed.

DNA and RNA Extraction

To study or manipulate nucleic acids, the DNA or RNA must first be isolated or extracted from the cells. This can be done through various techniques. Most nucleic acid extraction techniques involve steps to break open the cell and use enzymatic reactions to destroy all macromolecules that are not desired (such as degradation of unwanted molecules and separation from the DNA sample). Cells are broken using a lysis buffer (a solution that is mostly a detergent); lysis means “to split.” These enzymes break apart lipid molecules in the membranes of the cell and the nucleus. Macromolecules are inactivated using enzymes such as proteases that break down proteins, and ribonucleases (RNAses) that break down RNA. The DNA is then precipitated using alcohol. Human genomic DNA is usually visible as a gelatinous, white mass. Samples can be stored at –80°C for years.

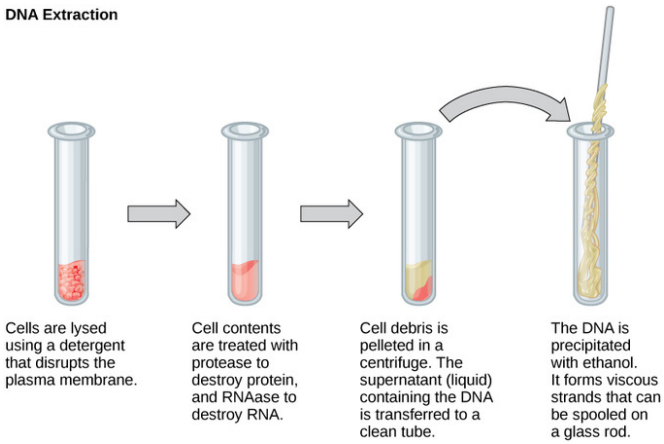

Figure: **DNA Extraction**: This diagram shows the basic method used for extraction of DNA.

RNA analysis is performed to study gene expression patterns in cells. RNA is naturally very unstable because RNAses are commonly present in nature and very difficult to inactivate. Similar to DNA, RNA extraction involves the use of various buffers and enzymes to inactivate macromolecules and preserve the RNA.

Gel Electrophoresis

Because nucleic acids are negatively-charged ions at neutral or basic pH in an aqueous environment, they can be mobilized by an electric field. Gel electrophoresis is a technique used to separate molecules on the basis of size using this charge and may be separated as whole chromosomes or fragments. The nucleic acids are loaded into a slot near the negative electrode of a porous gel matrix and pulled toward the positive electrode at the opposite end of the gel. Smaller molecules move through the pores in the gel faster than larger molecules; this difference in the rate of migration separates the fragments on the basis of size. There are molecular-weight standard samples that can be run alongside the molecules to provide a size comparison. Nucleic acids in a gel matrix can be observed using various fluorescent or colored dyes. Distinct nucleic acid fragments appear as bands at specific distances from the top of the gel (the negative electrode end) on the basis of their size.

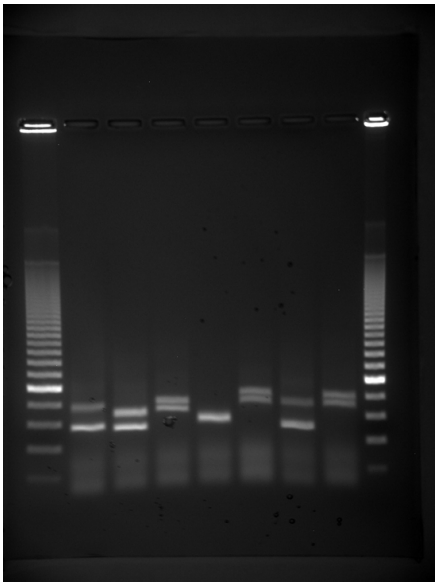

Figure: **Gel Electrophoresis**: Shown are DNA fragments from seven samples run on a gel, stained with a fluorescent dye, and viewed under UV light.

Amplification of Nucleic Acid Fragments by Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a technique used to amplify specific regions of DNA for further analysis. PCR is used for many purposes in laboratories, such as the cloning of gene fragments to analyze genetic diseases, identification of contaminant foreign DNA in a sample, and the amplification of DNA for sequencing. More practical applications include the determination of paternity and detection of genetic diseases.

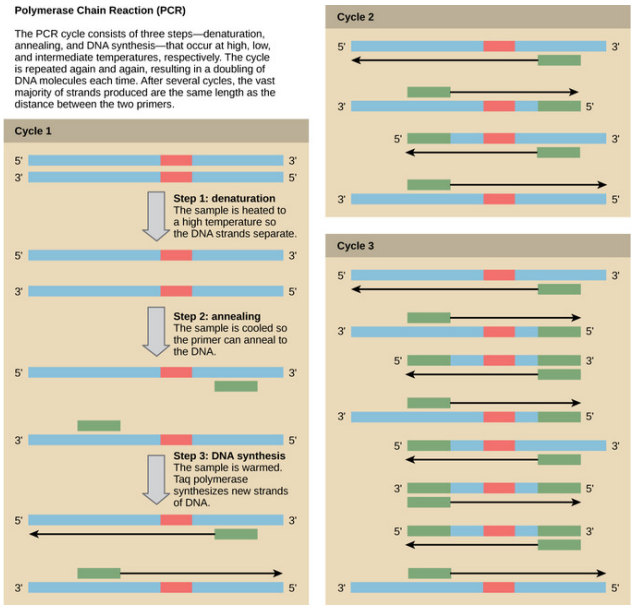

Figure: **PCR Amplification**: Polymerase chain reaction, or PCR, is used to amplify a specific sequence of DNA. Primers—short pieces of DNA complementary to each end of the target sequence—are combined with genomic DNA, Taq polymerase, and deoxynucleotides. Taq polymerase is a DNA polymerase isolated from the thermostable bacterium Thermus aquaticus that is able to withstand the high temperatures used in PCR. Thermus aquaticus grows in the Lower Geyser Basin of Yellowstone National Park. Reverse transcriptase PCR (RT-PCR) is similar to PCR, but cDNA is made from an RNA template before PCR begins.

DNA fragments can also be amplified from an RNA template in a process called reverse transcriptase PCR (RT-PCR). The first step is to recreate the original DNA template strand (called cDNA) by applying DNA nucleotides to the mRNA. This process is called reverse transcription. This requires the presence of an enzyme called reverse transcriptase. After the cDNA is made, regular PCR can be used to amplify it.

Hybridization, Southern Blotting, and Northern Blotting

Nucleic acid samples, such as fragmented genomic DNA and RNA extracts, can be probed for the presence of certain sequences. Short DNA fragments called probes are designed and labeled with radioactive or fluorescent dyes to aid detection. Gel electrophoresis separates the nucleic acid fragments according to their size. The fragments in the gel are then transferred onto a nylon membrane in a procedure called blotting. The nucleic acid fragments that are bound to the surface of the membrane can then be probed with specific radioactively- or fluorescently-labeled probe sequences. When DNA is transferred to a nylon membrane, the technique is called Southern blotting; when RNA is transferred to a nylon membrane, it is called northern blotting. Southern blots are used to detect the presence of certain DNA sequences in a given genome, and northern blots are used to detect gene expression.

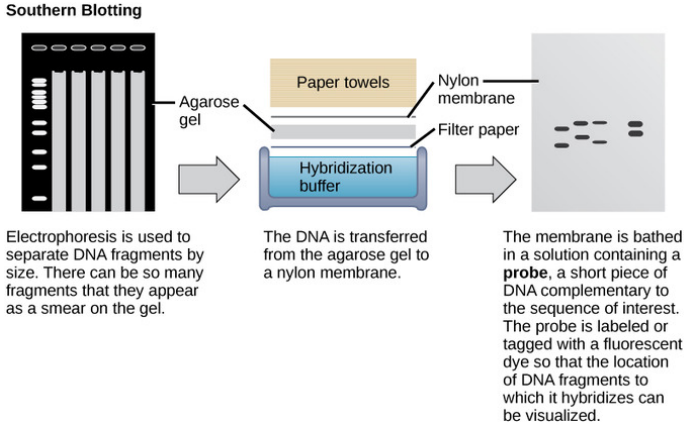

Figure: **Blotting Techniques**: Southern blotting is used to find a particular sequence in a sample of DNA. DNA fragments are separated on a gel, transferred to a nylon membrane, and incubated with a DNA probe complementary to the sequence of interest. Northern blotting is similar to Southern blotting, but RNA is run on the gel instead of DNA. In western blotting, proteins are run on a gel and detected using antibodies.

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7.12F: Molecular and Cellular Cloning

Molecular cloning reproduces the desired regions or fragments of a genome, enabling the manipulation and study of genes.

LEARNING OBJECTIVES

Describe the process of molecular cloning

Key Takeaways

Key Points

- Cloning small fragments of a genome allows specific genes, their protein products, and non-coding regions to be studied in isolation.
- A plasmid, also known as a vector, is a small circular DNA molecule that replicates independently of the chromosomal DNA; it can be used to provide a “folder” in which to insert a desired DNA fragment.
- Recombinant DNA molecules are plasmids with foreign DNA inserted into them; they are created artificially as they do not occur in nature.
- Bacteria and yeast naturally produce clones of themselves when they replicate asexually through cellular cloning.

Key Terms

- **recombinant DNA**: DNA that has been engineered by splicing together fragments of DNA from multiple species and introduced into the cells of a host
- **molecular cloning**: a biological method that creates many identical DNA molecules and directs their replication within a host organism
- **plasmid**: a circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa

Molecular Cloning

In general, the word “cloning” means the creation of a perfect replica; however, in biology, the re-creation of a whole organism is referred to as “reproductive cloning.” Long before attempts were made to clone an entire organism, researchers learned how to reproduce desired regions or fragments of the genome, a process that is referred to as molecular cloning.

Cloning small fragments of the genome allows for the manipulation and study of specific genes (and their protein products) or noncoding regions in isolation. A plasmid (also called a vector) is a small circular DNA molecule that replicates independently of the chromosomal DNA. In cloning, the plasmid molecules can be used to provide a “folder” in which to insert a desired DNA fragment. Plasmids are usually introduced into a bacterial host for proliferation. In the bacterial context, the fragment of DNA from the human genome (or the genome of another organism that is being studied) is referred to as foreign DNA (or a transgene) to differentiate it from the DNA of the bacterium, which is called the host DNA.

Plasmids occur naturally in bacterial populations (such as *Escherichia coli*) and have genes that can contribute favorable traits to the organism such as antibiotic resistance (the ability to be unaffected by antibiotics). Plasmids have been repurposed and engineered as vectors for molecular cloning and the large-scale production of important reagents such as insulin and human growth hormone. An important feature of plasmid vectors is the ease with which a foreign DNA fragment can be introduced via the multiple cloning site (MCS). The MCS is a short DNA sequence containing multiple sites that can be cut with different commonly-available restriction endonucleases. Restriction endonucleases recognize specific DNA sequences and cut them in a predictable manner; they are naturally produced by bacteria as a defense mechanism against foreign DNA. Many restriction endonucleases make staggered cuts in the two strands of DNA, such that the cut ends have a 2- or 4-base single-stranded overhang. Because these overhangs are capable of annealing with complementary overhangs, these are called “sticky ends.” Addition of an enzyme called DNA ligase permanently joins the DNA fragments via phosphodiester bonds. In this way, any DNA fragment generated by restriction endonuclease cleavage can be spliced between the two ends of a plasmid DNA that has been cut with the same restriction endonuclease.

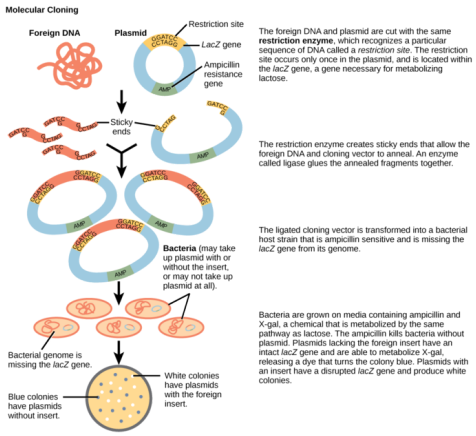

Figure: **Molecular Cloning**: This diagram shows the steps involved in molecular cloning, where regions or fragments of a genome are reproduced to allow the study or manipulation of genes and their protein products.

Recombinant DNA Molecules

Plasmids with foreign DNA inserted into them are called recombinant DNA molecules because they are created artificially and do not occur in nature. They are also called chimeric molecules because the origin of different parts of the molecules can be traced back to different species of biological organisms or even to chemical synthesis. Proteins that are expressed from recombinant DNA molecules are called recombinant proteins. Not all recombinant plasmids are capable of expressing genes. The recombinant DNA may need to be moved into a different vector (or host) that is better designed for gene expression. Plasmids may also be engineered to express proteins only when stimulated by certain environmental factors so that scientists can control the expression of the recombinant proteins.

Cellular Cloning

Unicellular organisms, such as bacteria and yeast, naturally produce clones of themselves when they replicate asexually by binary fission; this is known as cellular cloning. The nuclear DNA duplicates by the process of mitosis, which creates an exact replica of the genetic material.

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7.12G: Plasmids as Cloning Vectors

Plasmids can be used as cloning vectors, allowing the insertion of exogenous DNA into a bacterial target.

LEARNING OBJECTIVES

Illustrate how plasmids can be used as cloning vectors

Key Takeaways

Key Points

- All engineered vectors have an origin of replication, a multi- cloning site, and a selectable marker.
- Expression vectors (expression constructs) express the transgene in the target cell, and they have a promoter sequence that drives expression of the transgene.
- Transcription is needed for a plasmid to function, without the proper sequences to transcribe parts of a plasmid it will not be expressed or even maintained in host cells.
- Vectors can have many additional sequences that can be used for downstream applications—purification of proteins encoded by the plasmid and expressing proteins targeted to be exported or to a certain compartment of the cell.

Key Terms

- **Kozak sequence**: a sequence which occurs on eukaryotic mRNA and has the consensus (gcc)gccRccAUGG. The Kozak consensus sequence plays a major role in the initiation of the translation process. The sequence was named after the person who brought it to prominence, Marilyn Kozak.
- **transcription**: The synthesis of RNA under the direction of DNA.
- **polyadenylation**: The formation of a polyadenylate, especially that of a nucleic acid

Vectors

In molecular biology, a vector is a DNA molecule used as a vehicle to transfer foreign genetic material into another cell. The four major types of vectors are plasmids, viral vectors, cosmids, and artificial chromosomes. All engineered vectors have an origin of replication, a multi-cloning site, and a selectable marker. The vector itself is generally a DNA sequence that consists of an insert (transgene) and a larger sequence, which serves as the “backbone” of the vector. The purpose of a vector that transfers genetic information to another cell is typically to isolate, multiply, or express the insert in the target cell. Vectors called expression vectors (expression constructs) express the transgene in the target cell, and they generally have a promoter sequence that drives expression of the transgene.

Plasmids

Plasmids are double-stranded, generally circular DNA sequences capable of automatically replicating in a host cell. Plasmid vectors minimally consist of the transgene insert and an origin of replication, which allows for semi-independent replication of the plasmid in the host. Modern plasmids generally have many more features, notably a “multiple cloning site”—with nucleotide overhangs for insertion of an insert—and multiple restriction enzyme consensus sites on either side of the insert. Plasmids may be conjugative/transmissible or non-conjugative. Conjugative plasmids mediate DNA transfer through conjugation and therefore spread rapidly among the bacterial cells of a population. Nonconjugative plasmids do not mediate DNA through conjugation.

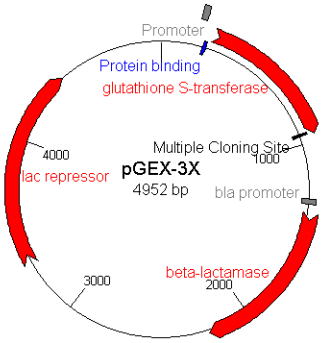

Figure: **Bacterial Cloning Vector**: The pGEX-3x plasmid is a popular cloning vector. The various elements of the plasmid are labelled.

Transcription

Transcription is a necessary component in all vectors. The purpose of a vector is to multiply the insert, although expression vectors also drive the translation of the multiplied insert. Even stable expression is determined by stable transcription, which depends on promoters in the vector. However, expression vectors have a two expression patterns: constitutive (consistent expression) or inducible (expression only under certain conditions or chemicals). Expression is based on different promoter activities, not post-transcriptional activities, meaning these two different types of expression vectors depend on different types of promoters. Expression vectors require translation of the vector's insert, thus requiring more components than simpler transcription-only vectors.

Expression vectors require sequences that encode for:

- A polyadenylation tail at the end of the transcribed pre-mRNA: This protects the mRNA from exonucleases and ensures transcriptional and translational termination and stabilizes mRNA production.
- Minimal UTR length: UTRs contain specific characteristics that may impede transcription or translation, so the shortest UTRs are encoded for in optimal expression vectors.
- Kozak sequence: a vector should encode for a Kozak sequence in the mRNA, which assembles the ribosome for translation of the mRNA.

The above conditions are necessary for expression vectors in eukaryotes, not prokaryotes.

Modern vectors may encompass additional features besides the transgene insert and a backbone:

- Promoter: a necessary component for all vectors, used to drive transcription of the vector's transgene.
- Genetic markers: Genetic markers for viral vectors allow for confirmation that the vector has integrated with the host genomic DNA.
- Antibiotic resistance: Vectors with antibiotic-resistance allow for survival of cells that have taken up the vector in growth media containing antibiotics through antibiotic selection.
- Epitope: A vector containing a sequence for a specific epitope that is incorporated into the expressed protein. Allows for antibody identification of cells expressing the target protein.
- Reporter genes: Some vectors may contain a reporter gene that allow for identification of plasmid that contains inserted DNA sequence. An example is lacZ-α which codes for the N-terminus fragment of β-galactosidase, an enzyme that digests galactose.
- Targeting sequence: Expression vectors may include encoding for a targeting sequence in the finished protein that directs the expressed protein to a specific organelle in the cell or specific location such as the periplasmic space of bacteria.
- Protein purification tags: Some expression vectors include proteins or peptide sequences that allows for easier purification of the expressed protein. Examples include polyhistidine-tag, glutathione-S-transferase, and maltose binding protein. Some of these tags may also allow for increased solubility of the target protein. The target protein is fused to the protein tag, but a protease cleavage site positioned in the polypeptide linker region between the protein and the tag allows the tag to be removed later.

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SECTION OVERVIEW

7.13: Bioinformatics

Topic hierarchy

7.13A: Strategies Used in Sequencing Projects

7.13B: Annotating Genomes

7.13C: Homologs, Orthologs, and Paralogs

7.13D: Synthesizing DNA

7.13E: Amplifying DNA - The Polymerase Chain Reaction

7.13F: DNA Sequencing Based on Sanger Dideoxynucleotides

7.13G: Metagenomics

7.13H: Reporter Fusions

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7.13A: Strategies Used in Sequencing Projects

The strategies used for sequencing genomes include the Sanger method, shotgun sequencing, pairwise end, and next-generation sequencing.

LEARNING OBJECTIVES

Compare the different strategies used for whole-genome sequencing: Sanger method, shotgun sequencing, pairwise-end sequencing, and next-generation sequencing

Key Takeaways

Key Points

- The Sanger method is a basic sequencing technique that uses fluorescently-labeled dideoxynucleotides (ddNTPs) during DNA replication which results in multiple short strands of replicated DNA that terminate at different points, based on where the ddNTP was incorporated.
- Shotgun sequencing is a method that randomly cuts DNA fragments into smaller pieces and then, with the help of a computer, takes the DNA fragments, analyzes them for overlapping sequences, and reassembles the entire DNA sequence.
- Pairwise-end sequencing is a type of shotgun sequencing which is used for larger genomes and analyzes both ends of the DNA fragments for overlap.
- Next-generation sequencing is a type of sequencing which is automated and relies on sophisticated software for rapid DNA sequencing.

Key Terms

- **fluorophore**: a molecule or functional group which is capable of fluorescence
- **contig**: a set of overlapping DNA segments, derived from a single source of genetic material, from which the complete sequence may be deduced
- **dideoxynucleotide**: any nucleotide formed from a deoxynucleotide by loss of an a second hydroxyl group from the deoxyribose group

Strategies Used in Sequencing Projects

The basic sequencing technique used in all modern day sequencing projects is the chain termination method (also known as the dideoxy method), which was developed by Fred Sanger in the 1970s. The chain termination method involves DNA replication of a single-stranded template with the use of a primer and a regular deoxynucleotide (dNTP), which is a monomer, or a single unit, of DNA. The primer and dNTP are mixed with a small proportion of fluorescently-labeled dideoxynucleotides (ddNTPs). The ddNTPs are monomers that are missing a hydroxyl group (–OH) at the site at which another nucleotide usually attaches to form a chain. Each ddNTP is labeled with a different color of fluorophore. Every time a ddNTP is incorporated in the growing complementary strand, it terminates the process of DNA replication, which results in multiple short strands of replicated DNA that are each terminated at a different point during replication. When the reaction mixture is processed by gel electrophoresis after being separated into single strands, the multiple, newly-replicated DNA strands form a ladder due to their differing sizes. Because the ddNTPs are fluorescently labeled, each band on the gel reflects the size of the DNA strand and the ddNTP that terminated the reaction. The different colors of the fluorophore-labeled ddNTPs help identify the ddNTP incorporated at that position. Reading the gel on the basis of the color of each band on the ladder produces the sequence of the template strand.

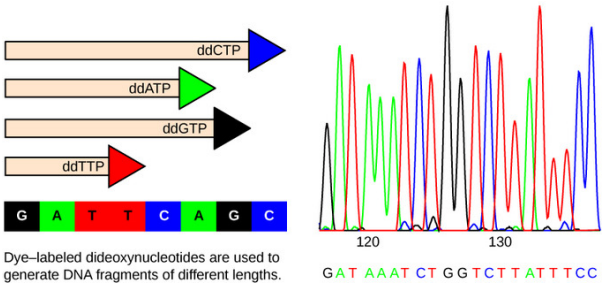
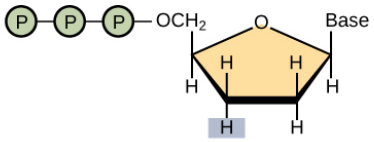
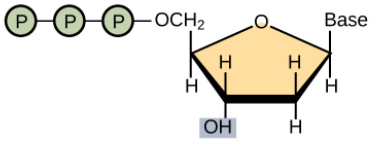


Figure: **Sanger's Method**: Frederick Sanger's dideoxy chain termination method uses dideoxynucleotides, in which the DNA fragment can be terminated at different points. The DNA is separated on the basis of size, and these bands, based on the size of the fragments, can be read.



Dideoxynucleotide (ddNTP)



Deoxynucleotide (dNTP)

Figure: **Structure of a Dideoxynucleotide**: A dideoxynucleotide is similar in structure to a deoxynucleotide, but is missing the 3′ hydroxyl group (indicated by the box). When a dideoxynucleotide is incorporated into a DNA strand, DNA synthesis stops.

Early Strategies: Shotgun Sequencing and Pair-Wise End Sequencing

In the shotgun sequencing method, several copies of a DNA fragment are cut randomly into many smaller pieces (somewhat like what happens to a round shot cartridge when fired from a shotgun). All of the segments are then sequenced using the chain-sequencing method. Then, with the help of a computer, the fragments are analyzed to see where their sequences overlap. By matching overlapping sequences at the end of each fragment, the entire DNA sequence can be reformed. A larger sequence that is assembled from overlapping shorter sequences is called a contig. As an analogy, consider that someone has four copies of a landscape photograph that you have never seen before and know nothing about how it should appear. The person then rips up each photograph with their hands, so that different size pieces are present from each copy. The person then mixes all of the pieces together and asks you to reconstruct the photograph. In one of the smaller pieces you see a mountain. In a larger piece, you see that the same mountain is behind a lake. A third fragment shows only the lake, but it reveals that there is a cabin on the shore of the lake. Therefore, from looking at the overlapping information in these three fragments, you know that the picture contains a mountain behind a lake that has a cabin on its shore. This is the principle behind reconstructing entire DNA sequences using shotgun sequencing.

Originally, shotgun sequencing only analyzed one end of each fragment for overlaps. This was sufficient for sequencing small genomes. However, the desire to sequence larger genomes, such as that of a human, led to the development of double-barrel shotgun sequencing, more formally known as pairwise-end sequencing. In pairwise-end sequencing, both ends of each fragment are analyzed for overlap. Pairwise-end sequencing is, therefore, more cumbersome than shotgun sequencing, but it is easier to reconstruct the sequence because there is more available information.

Next-generation Sequencing

Since 2005, automated sequencing techniques used by laboratories are under the umbrella of next-generation sequencing, which is a group of automated techniques used for rapid DNA sequencing. These automated, low-cost sequencers can generate sequences of hundreds of thousands or millions of short fragments (25 to 500 base pairs) in the span of one day. Sophisticated software is used to manage the cumbersome process of putting all the fragments in order.

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7.13B: Annotating Genomes

Genome annotation is the identification and understanding of the genetic elements of a sequenced genome.

LEARNING OBJECTIVES

Define genome annotation

Key Takeaways

Key Points

- Once a genome is sequenced, all of the sequencings must be analyzed to understand what they mean.
- Critical to annotation is the identification of the genes in a genome, the structure of the genes, and the proteins they encode.
- Once a genome is annotated, further work is done to understand how all the annotated regions interact with each other.

Key Terms

- **BLAST**: In bioinformatics, Basic Local Alignment Search Tool, or BLAST, is an algorithm for comparing primary biological sequence information, such as the amino-acid sequences of different proteins or the nucleotides of DNA sequences.
- **in silico**: In computer simulation or in virtual reality

Genome projects are scientific endeavors that ultimately aim to determine the complete genome sequence of an organism (be it an animal, a plant, a fungus, a bacterium, an archaean, a protist, or a virus). They annotate protein-coding genes and other important genome-encoded features. The genome sequence of an organism includes the collective DNA sequences of each chromosome in the organism. For a bacterium containing a single chromosome, a genome project will aim to map the sequence of that chromosome.

Once a genome is sequenced, it needs to be annotated to make sense of it. An annotation (irrespective of the context) is a note added by way of explanation or commentary. Since the 1980's, molecular biology and bioinformatics have created the need for DNA annotation. DNA annotation or genome annotation is the process of identifying the locations of genes and all of the coding regions in a genome and determining what those genes do.

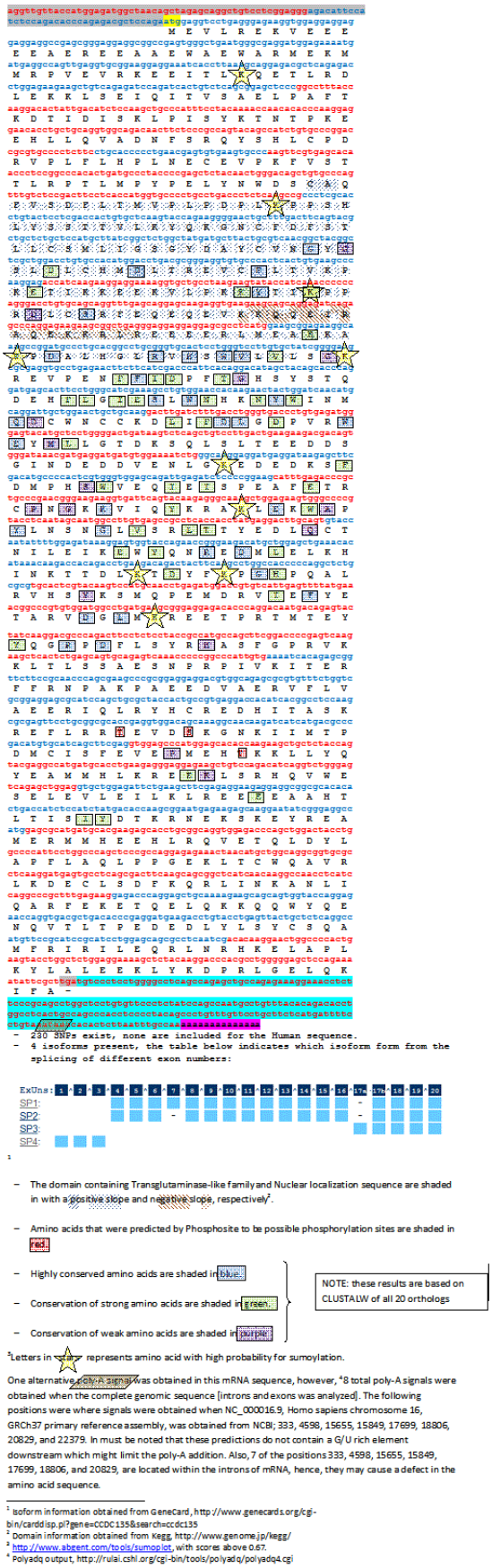

Figure: **Genome Annotation**: Here a small region of genome is annotated, with various elements identified. The annotation of an

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entire genome would entail a similar in depth analysis of thousand even millions of such DNA sequences.

Genome annotation is the process of attaching biological information to sequences. It consists of two main steps: identifying elements on the genome, a process called gene prediction, and attaching biological information to these elements. Automatic annotation tools try to perform all of this by computer analysis, as opposed to manual annotation (a.k.a. curation) which involves human expertise. Ideally, these approaches co-exist and complement each other in the same annotation pipeline (process). The basic level of annotation is using BLAST for finding similarities, and then annotating genomes based on that. However, nowadays more and more additional information is added to the annotation platform. The additional information allows manual annotators to deconvolute discrepancies between genes that are given the same annotation. Some databases use genome context information, similarity scores, experimental data, and integrations of other resources to provide genome annotations through their Subsystems approach. Other databases rely on both curated data sources as well as a range of different software tools in their automated genome annotation pipeline.

Structural annotation consists of the identification of genomic elements: ORFs and their localization, gene structure, coding regions, and the location of regulatory motifs. Functional annotation consists of attaching biological information to genomic elements: biochemical function, biological function, involved regulation and interactions, and expression.

These steps may involve both biological experiments and in silico analysis. Proteogenomics based approaches utilize information from expressed proteins, often derived from mass spectrometry, to improve genomics annotations. A variety of software tools have been developed to permit scientists to view and share genome annotations. Genome annotation is the next major challenge for the Human Genome Project, now that the genome sequences of human and several model organisms are largely complete. Identifying the locations of genes and other genetic control elements is often described as defining the biological “parts list” for the assembly and normal operation of an organism. Scientists are still at an early stage in the process of delineating this parts list and in understanding how all the parts “fit together. ”

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7.13C: Homologs, Orthologs, and Paralogs

Learning Objectives

- Distinguish homologs, orthologs and paralogs

Homology forms the basis of organization for comparative biology. A homologous trait is often called a homolog (also spelled homologue). In genetics, the term “homolog” is used both to refer to a homologous protein and to the gene (DNA sequence) encoding it. As with anatomical structures, homology between protein or DNA sequences is defined in terms of shared ancestry. Two segments of DNA can have shared ancestry because of either a speciation event (orthologs) or a duplication event (paralogs). Homology among proteins or DNA is often incorrectly concluded on the basis of sequence similarity. The terms “percent homology” and “sequence similarity” are often used interchangeably. As with anatomical structures, high sequence similarity might occur because of convergent evolution, or, as with shorter sequences, because of chance. Such sequences are similar, but not homologous. Sequence regions that are homologous are also called conserved. This is not to be confused with conservation in amino acid sequences in which the amino acid at a specific position has been substituted with a different one with functionally equivalent physicochemical properties. One can, however, refer to partial homology where a fraction of the sequences compared (are presumed to) share descent, while the rest does not. For example, partial homology may result from a gene fusion event.

```
AAB24882        TYHMCQFHCRYVNNHSGEKLYECNERSKAFSCPSHLQCHKRRQIGEKTHEHNQCGKAFPT 60
AAB24881        --------------------YECNQCGKAFAQHSSLKCHYRTHIGEKPYECNQCGKAFSK 40
                                    ****: .***:  * *:** * :****.:* *******..

AAB24882        PSHLQYHERTHTGEKPYECHQCGQAFKKCSLLQRHKRTHTGEKPYE-CNQCGKAFAQ- 116
AAB24881        HSHLQCHKRTHTGEKPYECNQCGKAFSQHGLLQRHKRTHTGEKPYMNVINMVKPLHNS 98
                 **** *:************:***:**.: .***************    :  *.: :
```

Figure: **Example of Homologous DNA**: This is the sequence alignment of a homologous protein from two different species The “*” represent a conserved amino acid in the two proteins.

Homologous sequences are orthologous if they were separated by a speciation event: when a species diverges into two separate species, the copies of a single gene in the two resulting species are said to be orthologous. Orthologs, or orthologous genes, are genes in different species that originated by vertical descent from a single gene of the last common ancestor. For instance, the plant Flu regulatory protein is present both in *Arabidopsis* (multicellular higher plant) and *Chlamydomonas* (single cell green algae). The *Chlamydomonas* version is more complex: it crosses the membrane twice rather than once, contains additional domains, and undergoes alternative splicing. However, it can fully substitute the much simpler *Arabidopsis* protein, if transferred from algae to plant genome by means of gene engineering. Significant sequence similarity and shared functional domains indicate that these two genes are orthologous genes, inherited from the shared ancestor. Orthologous sequences provide useful information in taxonomic classification and phylogenetic studies of organisms. The pattern of genetic divergence can be used to trace the relatedness of organisms. Two organisms that are very closely related are likely to display very similar DNA sequences between two orthologs. Conversely, an organism that is further removed evolutionarily from another organism is likely to display a greater divergence in the sequence of the orthologs being studied.

Homologous sequences are paralogous if they were separated by a gene duplication event: if a gene in an organism is duplicated to occupy two different positions in the same genome, then the two copies are paralogous. Paralogous genes often belong to the same species, but this is not necessary. For example, the hemoglobin gene of humans and the myoglobin gene of chimpanzees are paralogs. Paralogs can be split into in-paralogs (paralogous pairs that arose after a speciation event) and out-paralogs (paralogous pairs that arose before a speciation event). Between species out-paralogs are pairs of paralogs that exist between two organisms due to duplication before speciation. Within species out-paralogs are pairs of paralogs that exist in the same organism, but whose duplication event happened after speciation. Paralogs typically have the same or similar function, but sometimes do not. Due to lack of the original selective pressure upon one copy of the duplicated gene, this copy is free to mutate and acquire new functions. Paralogous sequences provide useful insight into the way genomes evolve. The genes encoding myoglobin and hemoglobin are considered to be ancient paralogs. Similarly, the four known classes of hemoglobins (hemoglobin A, hemoglobin A2, hemoglobin B, and hemoglobin F) are paralogs of each other. While each of these proteins serves the same basic function of oxygen transport, they have already diverged slightly in function: fetal hemoglobin (hemoglobin F) has a higher affinity for oxygen than adult hemoglobin. However, function is not always conserved. Human angiogenin diverged from ribonuclease, for example, and while the two paralogs remain similar in tertiary structure, their functions within the cell are now quite different.

Key Points

- A homologous gene (or homolog) is a gene inherited in two species from a common ancestor. While homologous genes can be similar in sequence, similar sequences are not necessarily homologous.
- Orthologous are homologous genes where a gene diverges after a speciation event, but the gene and its main function are conserved.
- If a gene is duplicated in a species, the resulting duplicated genes are paralogs of each other, even though over time they might become different in sequence composition and function.

Key Terms

- **conserved**: In biology, conserved sequences are similar or identical sequences that occur within nucleic acid sequences (such as RNA and DNA sequences), protein sequences, protein structures.
- **selective pressure**: Any cause that reduces reproductive success in a proportion of a population, potentially exerts evolutionary pressure or selection pressure.

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7.13D: Synthesizing DNA

Learning Objectives

- Outline the methods and uses of DNA synthesis

To understand bacterial genetics, the underlying genetic material (i.e. DNA) must be understood. DNA must be synthesized to study genes, the sequence of genomes, and many other studies. This occurs in two fashions, by polymerase chain reaction (PCR) which is enzymatic and chemical synthesis. PCR is covered in another atom. Here we will focus on chemical synthesis of DNA, which is also known as oligonucleotide synthesis.

Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids, both DNA and RNA with a defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence. Whereas enzymes synthesize DNA and RNA in a 5′ to 3′ direction, chemical oligonucleotide synthesis is carried out in the opposite, 3′ to 5′ direction.

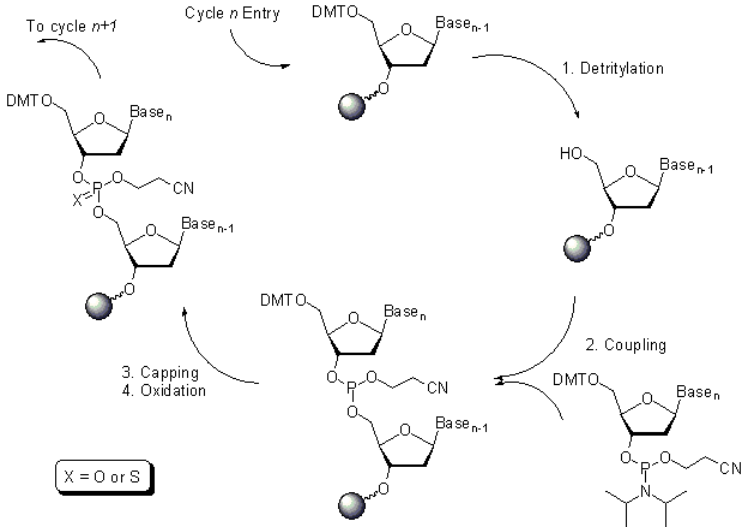

Figure: **Oligosynthesis.**: The complex chemical reactions that are needed to couple one nucleotide to another are outlined here.

Currently, the process is implemented as solid -phase synthesis using phosphoramidite method and phosphoramidite building blocks derived from protected 2′-deoxynucleosides (dA, dC, dG, and T), ribonucleosides (A, C, G, and U), or chemically modified nucleosides, e.g. LNA. To obtain the desired oligonucleotide, the building blocks are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. The process has been fully automated since the late 1970's. Upon the completion of the chain assembly, the product is released from the solid phase to solution, deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues) because the number of errors accumulates with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity. Typically, synthetic oligonucleotides are single-stranded DNA or RNA molecules around 15–25 bases in length. Oligonucleotides find a variety of applications in molecular biology and medicine. They are most commonly used as antisense oligonucleotides, small interfering RNA, primers for DNA sequencing and amplification, probes for detecting complementary DNA or RNA via molecular hybridization, tools for the targeted introduction of mutations and restriction sites, and for the synthesis of artificial genes.

A further application of oligosynthesis is to make artificial genes. Artificial gene synthesis is the process of synthesizing a gene in vitro without the need for initial template DNA samples. The main method is currently by oligonucleotide synthesis (also used for other applications) from digital genetic sequences and subsequent annealing of the resultant fragments. In contrast, natural DNA replication requires existing DNA templates for synthesizing new DNA.

Key Points

- DNA and RNA are at their essence chemical structures, and as such complex chemical reactions can be used to synthesize them.

- There are enzymatic ways to amplify DNA, notably PCR, while DNA sequences can be chemically synthesized by a process known as oligosynthesis.
- Oligosynthesis can be used to make artificial genes, which allows scientists to design and synthesis novel gene products, without relying a template of a gene found in nature.

Key Terms

- **phosphoramidite**: Any of a class of organic compounds formally derived from a phosphite by replacing a >P-O-R with a >P-N<R2 group; used in the synthesis of nucleic acids, etc.
- **HPLC**: High-performance liquid chromatography (sometimes referred to as high-pressure liquid chromatography), HPLC, is a chromatographic technique used to separate a mixture of compounds in analytical chemistry and biochemistry with the purpose of identifying, quantifying and purifying the individual components of the mixture.

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7.13E: Amplifying DNA - The Polymerase Chain Reaction

Learning Objectives

- Illustrate the applications, components and steps of PCR

The polymerase chain reaction (PCR) is a biochemical technology in molecular biology used to amplify a single, or a few copies, of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Applications

Developed in 1983 by Kary Mullis, PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications including the following:

- DNA cloning for sequencing; DNA-based phylogeny, or functional analysis of genes
- The diagnosis of hereditary diseases
- The identification of genetic fingerprints (used in forensic sciences and paternity testing)
- The detection and diagnosis of infectious diseases

The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments) containing sequences complementary to the target region, along with a DNA polymerase (after which the method is named) are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified. PCR can be extensively modified to perform a wide array of genetic manipulations.

Components

PCR is used to amplify a specific region of a DNA strand (the DNA target). Most PCR methods typically amplify DNA fragments of up to ~10 kilo base pairs (kb), although some techniques allow for amplification of fragments up to 40 kb in size. The reaction produces a limited amount of final amplified product that is governed by the available reagents in the reaction, and the feedback-inhibition of the reaction products. A basic PCR set up requires the following components and reagents:

- DNA template that contains the DNA region (target) to be amplified
- Two primers that are complementary to the 3′ (three prime) ends of each of the sense and anti-sense strand of the DNA target
- Taq polymerase or another DNA polymerase with a temperature optimum at around 70 °C
- Deoxynucleoside triphosphates (dNTPs; nucleotides containing triphosphate groups), the building-blocks from which the DNA polymerase synthesizes a new DNA strand
- Buffer solution, providing a suitable chemical environment for optimum activity and stability of the DNA polymerase.Divalent cations, magnesium or manganese ions; generally Mg^{2+}
- Monovalent cation potassium ions

Typically, PCR consists of a series of 20-40 repeated temperature changes, called cycles, with each cycle commonly consisting of two to three discrete temperature steps, usually three. The temperatures used, and the length of time they are applied in each cycle, depend on a variety of parameters. These include the enzyme used for DNA synthesis, the concentration of divalent ions and dNTPs in the reaction, and the melting temperature (Tm) of the primers.

Steps

The following are the steps of PCR:

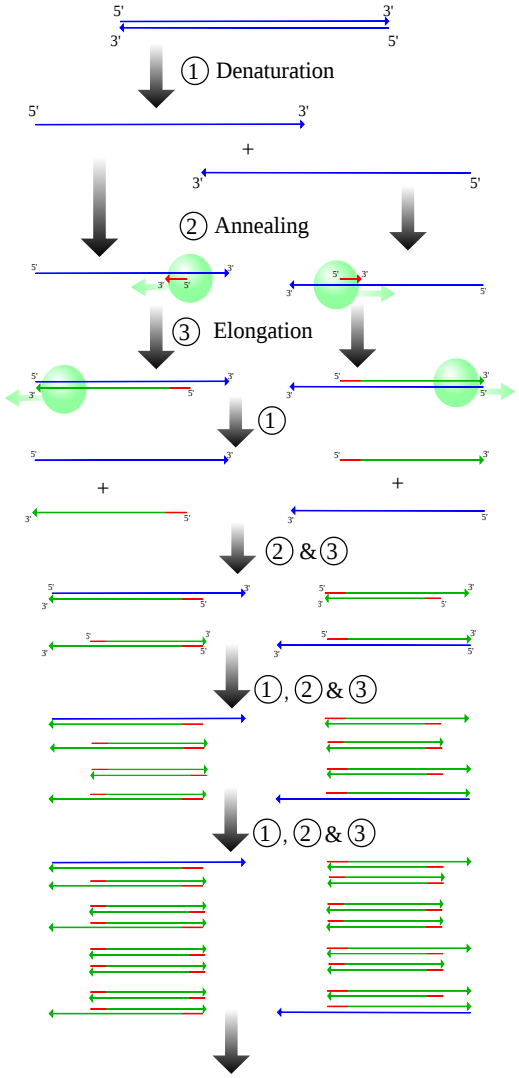

Figure: **The Steps of PCR**: This illustrates a PCR reaction to demonstrate how amplification leads to the exponential growth of a short product flanked by the primers. 1. Denaturing at 96°C. 2. Annealing at 68°C. 3. Elongation at 72°C. The first cycle is complete. The two resulting DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each new cycle.

1. Denaturation step: This step is the first regular cycling event and consists of heating the reaction to 94-98°C. It causes DNA melting of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules.
2. Annealing step: The reaction temperature is lowered to 50-65°C for 20-40 seconds allowing annealing of the primers to the single-stranded DNA template.
3. Extension/elongation step: The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5′ to 3′ direction, condensing the 5′-phosphate group of the dNTPs with the 3′-hydroxyl group at the end of the nascent (extending) DNA strand.

After elongation, the cycle goes back to step one, usually for 20-40 cycles. Under optimum conditions (i.e., if there are no limitations due to limiting substrates or reagents) at each extension step, the amount of DNA target is doubled, leading to exponential (geometric) amplification of the specific DNA fragment.

Key Points

- PCR is used to amplify a specific region of DNA.
- PCR typically consists of three steps: denaturation, annealing, and elongation.
- The amplified DNA can be used for many purposes, such as identifying different genes and species of bacteria.

Key Terms

- **annealing**: Annealing, in genetics, means for complementary sequences of single-stranded DNA or RNA to pair by hydrogen bonds to form a double-stranded polynucleotide. The term is often used to describe the binding of a DNA probe, or the binding of a primer to a DNA strand during a polymerase chain reaction (PCR). The term is also often used to describe the reformation (renaturation) of complementary strands that were separated by heat (thermally denatured). Proteins such as RAD52 can help DNA anneal.

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7.13F: DNA Sequencing Based on Sanger Dideoxynucleotides

Learning Objectives

- Recall dideoxynucleotide sequencing

Sanger sequencing, also known as chain-termination sequencing, refers to a method of DNA sequencing developed by Frederick Sanger in 1977. This method is based on amplification of the DNA fragment to be sequenced by DNA polymerase and incorporation of modified nucleotides – specifically, dideoxynucleotides (ddNTPs).

The classical chain-termination method requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated. The ddNTPs may be radioactively or fluorescently labelled for detection in automated sequencing machines.The DNA sample is divided into four separate sequencing reactions, containing all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP) and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP). Following rounds of template DNA extension from the bound primer, the resulting DNA fragments are heat denatured and separated by size using gel electrophoresis. This is frequently performed using a denaturing polyacrylamide-urea gel with each of the four reactions run in one of four individual lanes (lanes A, T, G, C). The DNA bands may then be visualized by autoradiography or UV light and the DNA sequence can be directly read off the X-ray film or gel image.

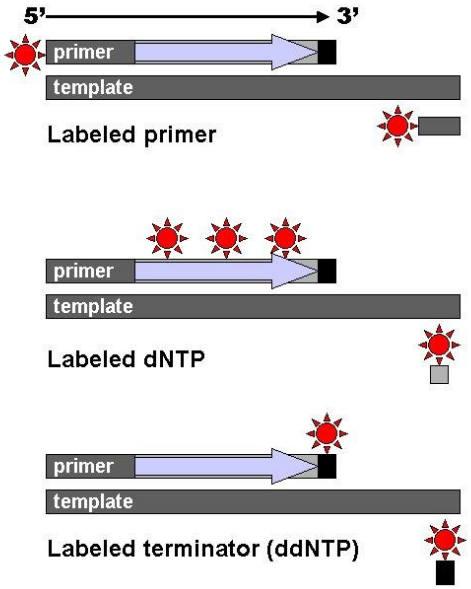

Figure: **Sanger sequencing**: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

Technical variations of chain-termination sequencing include tagging with nucleotides containing radioactive phosphorus for radiolabelling, or using a primer labeled at the 5′ end with a fluorescent dye. Dye-primer sequencing facilitates reading in an optical system for faster and more economical analysis and automation. The later development by Leroy Hood and coworkers of fluorescently labeled ddNTPs and primers set the stage for automated, high-throughput DNA sequencing. Chain-termination methods have greatly simplified DNA sequencing. More recently, dye-terminator sequencing has been developed. Dye-terminator sequencing utilizes labelling of the chain terminator ddNTPs, which permits sequencing in a single reaction, rather than four reactions as in the labelled-primer method. In dye-terminator sequencing, each of the four dideoxynucleotide chain terminators is labelled with fluorescent dyes, each of which emit light at different wavelengths.

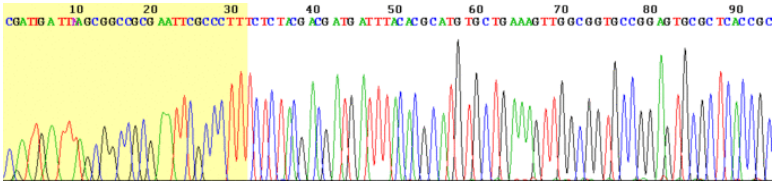

Figure: **Chromatograph**: This is an example of the output of a Sanger sequencing read using fluorescently labelled dye-terminators. The four DNA bases are represented by different colours which are interpreted by the software to give the DNA sequence above.

Automated DNA-sequencing instruments (DNA sequencers) can sequence up to 384 DNA samples in a single batch (run) in up to 24 runs a day. DNA sequencers carry out capillary electrophoresis for size separation, detection and recording of dye fluorescence, and data output as fluorescent peak trace chromatograms. Automation has lead to the sequencing of entire genomes.

Key Points

- The lack of the second deoxy group on an dNTP making it ddNTP, stops the incorporation of further nucleotides, this termination creates DNA lengths stopped at every nucleotide, this is central to further identifying each nucleotide.
- Different labels can be used, ddNTPS, dNTPs and primers can all be labelled with radioactivity and fluorescently.
- Using fluorescent labels, dideoxy sequencing can be automated allowing high-throughput methods which have been utilized to sequence entire genomes.

Key Terms

- **chromatogram**: The visual output from a chromatograph. Usually a graphical display or histogram.
- **dideoxynucleotide**: Any nucleotide formed from a deoxynucleotide by loss of an a second hydroxy group from the deoxyribose group

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7.13G: Metagenomics

Metagenomics is the study of genetic material derived from environmental samples.

LEARNING OBJECTIVES

Summarize the utility of metagenomics

Key Takeaways

Key Points

- While previous work needed cultivation of single microbes before they could be sequenced and identified, metagenomics attempts to more completely identify many of the microbes that inhabit a given environmental location.
- The first attempts at metagenomics was to sequence one gene from a sample. The changes in that one gene helped determine the microbial diversity in a sample.
- High-throughput sequencing allows the complete sequencing and assembly of entire genomes of the microbes that inhabit a given environment, giving unprecedented depth into understanding the microbial diversity of the world around us.

Key Terms

- **solid**: SOLiD (Sequencing by Oligonucleotide Ligation and Detection) is a next-generation DNA sequencing technology developed by Life Technologies and has been commercially available since 2008. This next generation technology generates hundreds of millions to billions of small sequence reads at one time.
- **gigabase**: One billion bases (nucleotides) as a unit of length of a nucleic acid
- **pyrosequencing**: A technique used to sequence DNA using chemiluminescent enzymatic reactions

Metagenomics

Metagenomics is the study of metagenomes; genetic material recovered directly from environmental samples. The broad field may also be referred to as environmental genomics, ecogenomics or community genomics. While traditional microbiology and microbial genome sequencing and genomics rely upon cultivated clonal cultures, early environmental gene sequencing cloned specific genes (often the 16S rRNA gene) to produce a profile of diversity in a natural sample. Such work revealed that the vast majority of microbial biodiversity had been missed by cultivation-based methods. Recent studies use “shotgun” Sanger sequencing or massively parallel pyrosequencing to get largely unbiased samples of all genes from all the members of the sampled communities. Due to its ability to reveal the previously hidden diversity of microscopic life, metagenomics offers a powerful lens for viewing the microbial world that has the potential to revolutionize understanding of the entire living world.

Conventional Sequencing Studies

Conventional sequencing begins with a culture of identical cells as a source of DNA. However, early metagenomic studies revealed that there are probably large groups of microorganisms in many environments that cannot be cultured and thus cannot be sequenced. These early studies focused on 16S ribosomal RNA sequences which are relatively short, often conserved within a species, and generally different between species. Many 16S rRNA sequences have been found which do not belong to any known cultured species, indicating that there are numerous non-isolated organisms. These surveys of ribosomal RNA (rRNA) genes taken directly from the environment revealed that cultivation based methods find less than 1% of the bacterial and archaeal species in a sample.

Shotgun Metagenomics

Advances in bioinformatics, refinements of DNA amplification, and the proliferation of computational power have greatly aided the analysis of DNA sequences recovered from environmental samples, This allows the adaptation of shotgun sequencing to metagenomic samples. The approach, used to sequence many cultured microorganisms and the human genome, randomly shears DNA, sequences many short sequences, and reconstructs them into a consensus sequence. Shotgun sequencing and screens of clone libraries reveal genes present in environmental samples. This provides information both on which organisms are present and what metabolic processes are possible in the community. This can be helpful in understanding the ecology of a community, particularly if multiple samples are compared to each other.

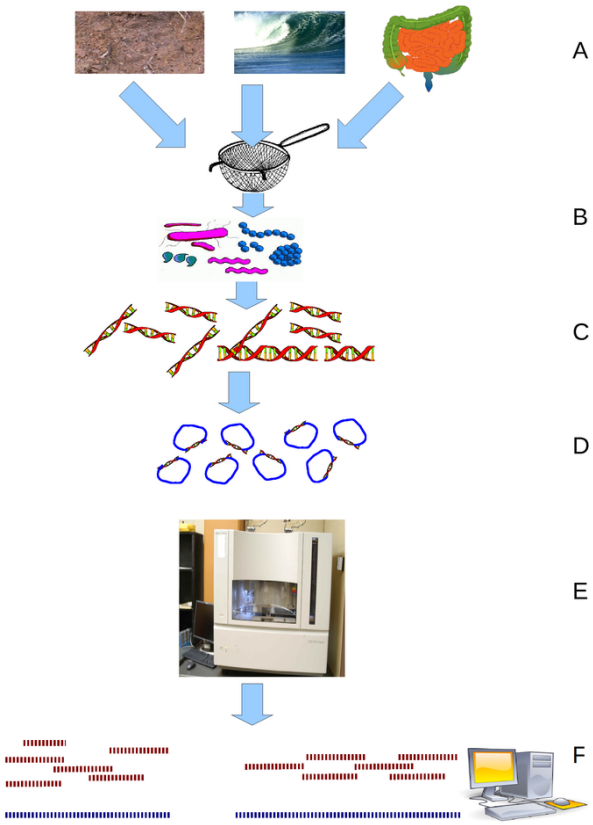

Figure: **Environmental Shotgun Sequencing (ESS)**: (A) sampling from habitat; (B) filtering particles, typically by size; (C) Lysis and DNA extraction; (D) cloning and library construction; (E) sequencing the clones; (F) sequence assembly into contigs and scaffolds

Shotgun metagenomics is also capable of sequencing nearly complete microbial genomes directly from the environment. As the collection of DNA from an environment is largely uncontrolled, the most abundant organisms in an environmental sample are most highly represented in the resulting sequence data. To achieve the high coverage needed to fully resolve the genomes of under-represented community members, large samples are needed. On the other hand, the random nature of shotgun sequencing ensures that many of these organisms, which would otherwise go unnoticed using traditional culturing techniques, will be represented by at least some small sequence segments.

High-Throughput Sequencing

The first metagenomic studies conducted using high-throughput sequencing used massively parallel 454 pyrosequencing. Two other technologies commonly applied to environmental sampling are the Illumina Genome Analyzer II and the Applied Biosystems SOLiD system. These techniques for sequencing DNA generate shorter fragments than Sanger sequencing; 454 pyrosequencing typically produces ~400 bp reads, Illumina and SOLiD produce 25-75 bp reads. These read lengths are significantly shorter than the typical Sanger sequencing read length of ~750 bp.

However, this limitation is compensated for by the much larger number of sequence reads. Pyrosequenced metagenomes generate 200–500 megabases, while Illumina platforms generate around 20–50 gigabases. An additional advantage to short read sequencing is that this technique does not require cloning the DNA before sequencing, removing one of the main biases in environmental sampling. As most short-read assembly software was not designed for metagenomic applications, specialized methods have been developed to utilize mate-read data in metagenomic assembly. From these studies the microbial fauna that might reside in a sample of soil, even on the surface of a keyboard, can be more accurately and efficiently identified.

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7.13H: Reporter Fusions

A reporter fusion is the hybrid of a gene or portion of a gene with a tractable marker.

LEARNING OBJECTIVES

Explain reporter fusions

Key Takeaways

Key Points

- A reporter construct allows the study of gene ‘s function and localization of a gene product.
- The promoter reporter constructs allow a protein to be expressed under the control of a target gene.
- Reporter fusions can fuse a protein of interest to a protein with a property of interest, therefore allowing the tagged protein to be further studied.

Key Terms

- **substrate analog**: Substrate analogs (substrate state analogues), are chemical compounds with a chemical structure that resemble the substrate molecule in an enzyme-catalyzed chemical reaction.
- **luminescent**: Emitting light by luminescence.

In molecular biology, a reporter gene (often simply reporter) is a gene that researchers attach to a regulatory sequence of another gene of interest in bacteria, cell culture, animals, or plants. Certain genes are chosen as reporters because the characteristics they confer on organisms expressing them are easily identified and measured, or because they are selectable markers. Reporter genes are often used as an indication of whether a certain gene has been taken up by or expressed in the cell or organism population.

To introduce a reporter gene into an organism, scientists place the reporter gene and the gene of interest in the same DNA construct to be inserted into the cell or organism. For bacteria or prokaryotic cells in culture, this is usually in the form of a circular DNA molecule called a plasmid. It is important to use a reporter gene that is not natively expressed in the cell or organism under study, since the expression of the reporter is being used as a marker for successful uptake of the gene of interest. Commonly used reporter genes that induce visually identifiable characteristics usually involve fluorescent and luminescent proteins. Examples include the gene that encodes jellyfish green fluorescent protein (GFP), which causes cells that express it to glow green under blue light, the enzyme luciferase, which catalyzes a reaction with luciferin to produce light, and the red fluorescent protein from the gene dsRed. A common reporter in bacteria is the E. coli lacZ gene, which encodes the protein beta-galactosidase. This enzyme causes bacteria expressing the gene to appear blue when grown on a medium that contains the substrate analog X-gal. An example of a selectable-marker which is also a reporter in bacteria is the chloramphenicol acetyltransferase (CAT) gene, which confers resistance to the antibiotic chloramphenicol.

Reporter genes can also be used to assay for the expression of the gene of interest, which may produce a protein that has little obvious or immediate effect on the cell culture or organism. In these cases the reporter is directly attached to the gene of interest to create a gene fusion. The two genes are under the same promoter elements and are transcribed into a single messenger RNA molecule. The mRNA is then translated into protein. In these cases it is important that both proteins be able to properly fold into their active conformations and interact with their substrates despite being fused. In building the DNA construct, a segment of DNA coding for a flexible polypeptide linker region is usually included so that the reporter and the gene product will only minimally interfere with one another. This is often done with GFP. The resulting protein-GFP hybrid transcribed from the reporter construct now has a protein attached to GFP. In the case of GFP which fluorescence one can deduce that the attached protein is wherever the fluorescence is. This allows a researched to determine where in a cell a protein may be localized in a cell.

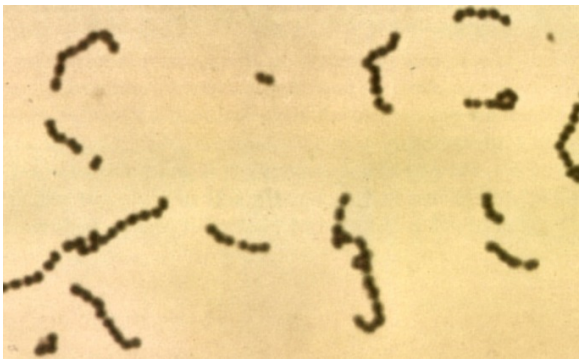

Figure: **Streptococci**: Light microscopy view of streptococci, a non-sporulating lactic acid bacteria.

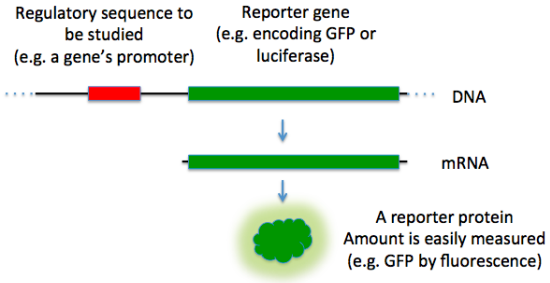

Figure: **Introducing a reporter gene into a cell**: In molecular biology, a reporter gene (often simply reporter) is a gene that researchers attach to a regulatory sequence of another gene of interest in bacteria, cell culture, animals, or plants

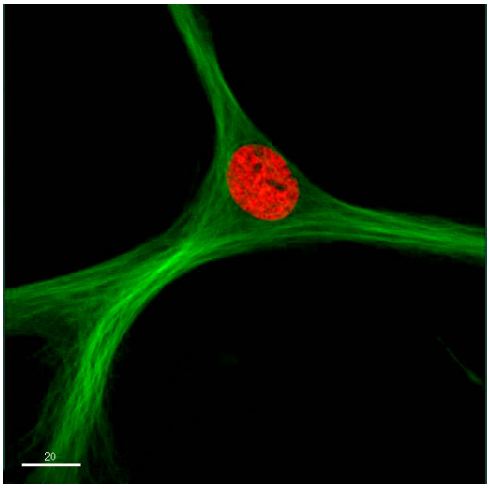

Figure: **GFP fusion proteins**: A human mesenchymal stem cell. In this cell a microtubule protein is fused to GFP (green) while a histone protein is fused to RFP (red). As you can see the localization of the fused protein can now be determined using fluorescent reporter fusions.

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SECTION OVERVIEW

7.14: Cloning Techniques

Topic hierarchy

7.14A: Putting Foreign DNA into Cells

7.14B: Obtaining DNA

7.14C: Hosts for Cloning Vectors

7.14D: Shuttle Vectors and Expression Vectors

7.14E: Bacteriophage Lambda as a Cloning Vector

7.14F: Vectors for Genomic Cloning and Sequencing

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7.14A: Putting Foreign DNA into Cells

The methods used to get DNA into cells are varied (e.g., transformation, transduction, transfection, and electroporation).

LEARNING OBJECTIVES

Describe the methods of introducing foreign DNA into cells

Key Takeaways

Key Points

- When microorganisms are able to take up and replicate DNA from their local environment, the process is termed transformation.
- In mammalian cell culture, the analogous process of introducing DNA into cells is commonly termed transfection.
- Electroporation uses high voltage electrical pulses to translocate DNA across the cell membrane (and cell wall, if present).

Key Terms

- **transformation**: The alteration of a bacterial cell caused by the transfer of DNA from another, especially if pathogenic.
- **microorganisms**: A microorganism or microbe is a microscopic organism that comprises either a single cell (unicellular), cell clusters, or multicellular relatively complex organisms.

The DNA mixture, previously manipulated in vitro, is moved back into a living cell, referred to as the host organism. The methods used to get DNA into cells are varied, and the name applied to this step in the molecular cloning process will often depend upon the experimental method that is chosen (e.g., transformation, transduction, transfection, electroporation).

When microorganisms are able to take up and replicate DNA from their local environment, the process is termed transformation, and cells that are in a physiological state such that they can take up DNA, are said to be competent. In mammalian cell culture, the analogous process of introducing DNA into cells is commonly termed transfection. Both transformation and transfection usually require preparation of the cells through a special growth regime and chemical treatment process that will vary with the specific species and cell types that are used.

Electroporation uses high voltage electrical pulses to translocate DNA across the cell membrane (and cell wall, if present). In contrast, transduction involves the packaging of DNA into virus-derived particles, and using these virus-like particles to introduce the encapsulated DNA into the cell through a process resembling viral infection. Although electroporation and transduction are highly specialized methods, they may be the most efficient methods to move DNA into cells.

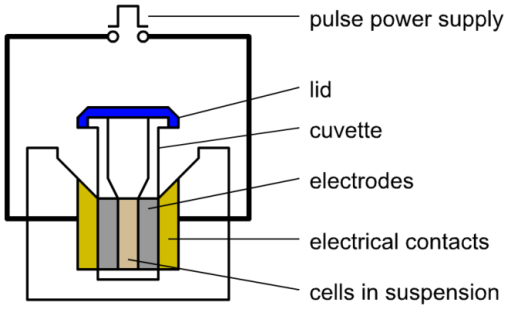

Figure: **Electroporation**: Diagram of the major components of an electroporator with cuvette loaded.

Whichever method is used, the introduction of recombinant DNA into the chosen host organism is usually a low efficiency process; that is, only a small fraction of the cells will actually take up DNA. Experimental scientists deal with this issue through a step of artificial genetic selection, in which cells that have not taken up DNA are selectively killed, and only those cells that can actively replicate DNA containing the selectable marker gene encoded by the vector are able to survive.

When bacterial cells are used as host organisms, the selectable marker is usually a gene that confers resistance to an antibiotic that would otherwise kill the cells, typically ampicillin. Cells harboring the vector will survive when exposed to the antibiotic, while those that have failed to take up vector sequences will die. When mammalian cells (e.g., human or mouse cells) are used, a similar strategy is used, except that the marker gene (in this case typically encoded as part of the kanMX cassette) confers resistance to the antibiotic Geneticin.

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7.14B: Obtaining DNA

When cloning genomic DNA, the DNA to be cloned is extracted from the organism of interest.

LEARNING OBJECTIVES

Explain the methods of obtaining DNA for molecular cloning experiments and the process of creating a recombinant DNA molecule

Key Takeaways

Key Points

- The cloning vector is treated with a restriction endonuclease to cleave the DNA at the site where foreign DNA will be inserted.
- DNA for cloning experiments may also be obtained from RNA using reverse transcriptase (complementary DNA or cDNA cloning), or in the form of synthetic DNA (artificial gene synthesis).
- The creation of recombinant DNA is in many ways the simplest step of the molecular cloning process.

Key Terms

- **DNA**: A biopolymer of deoxyribonucleic acids (a type of nucleic acid) that has four different chemical groups, called bases: adenine, guanine, cytosine, and thymine.
- **cloning**: The production of a cloned embryo by transplanting the nucleus of a somatic cell into an ovum.
- **cloning vector**: A cloning vector is a small piece of DNA, taken from a virus, a plasmid, or the cell of a higher organism, into which a foreign DNA fragment can be inserted.

Molecular cloning is a set of experimental methods in molecular biology that are used to assemble recombinant DNA molecules and to direct their replication within host organisms. The word cloning in this context refers to the fact that the method involves the replication of a single DNA molecule starting from a single living cell to generate a large population of cells containing identical DNA molecules. Molecular cloning generally uses DNA sequences from two different organisms: the species that is the source of the DNA to be cloned, and the species that will serve as the living host for replication of the recombinant DNA.

For cloning of genomic DNA, the DNA to be cloned is extracted from the organism of interest. Virtually any tissue source can be used (even tissues from extinct animals) as long as the DNA is not extensively degraded. The DNA is then purified using simple methods to remove contaminating proteins (extraction with phenol), RNA (ribonuclease) and smaller molecules (precipitation and/or chromatography). Polymerase chain reaction (PCR) methods are often used for amplification of specific DNA or RNA (by a process known as Reverse-Transcription or RT-PCR) sequences prior to molecular cloning using primers or short DNA sequences specific for the region of interest. DNA for cloning experiments may also be obtained from RNA using reverse transcriptase (complementary DNA or cDNA cloning), or in the form of synthetic DNA (artificial gene synthesis). cDNA cloning is usually used to obtain clones representative of the mRNA population of the cells of interest, while synthetic DNA is used to obtain any precise sequence defined by the designer.

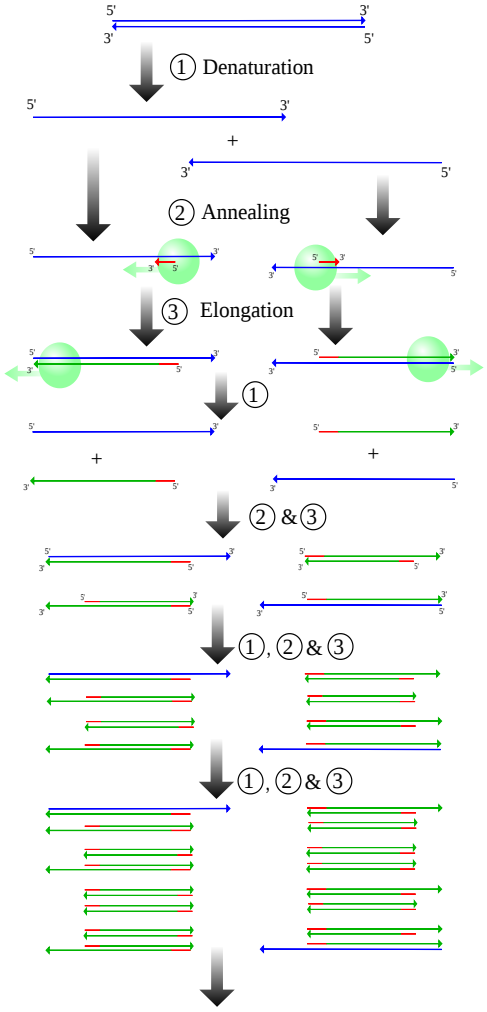

Figure: **The Steps of PCR**: This illustrates a PCR reaction to demonstrate how amplification leads to the exponential growth of a short product flanked by the primers. 1. Denaturing at 96°C. 2. Annealing at 68°C. 3. Elongation at 72°C. The first cycle is complete. The two resulting DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each new cycle.

Although a very large number of host organisms and molecular cloning vectors are used, the great majority of molecular cloning experiments begin with a laboratory strain of the bacterium E. coli (Escherichia coli) and a plasmid cloning vector. E. coli and plasmid vectors are in common use because they are technically sophisticated, versatile, widely available and offer rapid growth of recombinant organisms with minimal equipment. If the DNA to be cloned is exceptionally large (hundreds of thousands to millions of base pairs), then a bacterial artificial chromosome or yeast artificial chromosome vector is often chosen.

The cloning vector is treated with a restriction endonuclease to cleave the DNA at the site where foreign DNA will be inserted. The restriction enzyme is chosen to generate a configuration at the cleavage site that is compatible with that at the ends of the foreign DNA. Typically, this is done by cleaving the vector DNA and foreign DNA with the same restriction enzyme. Most modern vectors contain a variety of convenient cleavage sites that are unique within the vector molecule (so that the vector can only be cleaved at a single site) and are not located within the gene of interest to be cloned.

The creation of recombinant DNA is in many ways the simplest step of the molecular cloning process. DNA prepared from the vector and foreign source are treated with restriction enzymes to generate fragments with ends capable of being linked to those of the vector and they are simply mixed together at appropriate concentrations and exposed to an enzyme (DNA ligase) that covalently links the ends together. This joining reaction is often termed ligation. The resulting DNA mixture containing randomly joined ends is then ready for introduction into the host organism for amplification (a process known as transformation). In

mammalian cell culture, the analogous process of introducing DNA into cells is commonly known as transfection. Both transformation and transfection usually require preparation of the cells through a special growth regimen and chemical treatment process that will vary with the specific species and cell types that are used. Whichever method is used, the introduction of recombinant DNA into the chosen host organism is usually a low efficiency process; that is, only a small fraction of the cells will actually take up DNA. When bacterial cells are used as host organisms, the selectable marker is usually a gene that confers resistance to an antibiotic, typically ampicillin, that would otherwise kill the cells. Cells harboring the cloning vector will survive when exposed to the antibiotic, while those that have failed to take up cloning vector will die. The former can therefore be amplified and screened for the presence of the gene of interest in the cloning vector by restriction digest analysis.

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7.14C: Hosts for Cloning Vectors

The majority of molecular cloning experiments begin with a laboratory strain of the bacterium *E. coli* (*Escherichia coli*) as the host.

LEARNING OBJECTIVES

Describe the features of a typical cloning vector

Key Takeaways

Key Points

- *E. coli* and plasmid vectors are in common use because they are technically sophisticated, versatile, widely available, and offer rapid growth of recombinant organisms with minimal equipment.
- If the DNA to be cloned is exceptionally large, then a bacterial artificial chromosome or yeast artificial chromosome vector is often chosen.
- Specialized applications may call for specialized host -vector systems.

Key Terms

- **Escherichia coli**: Escherichia coli is a Gram-negative, rod-shaped bacterium that is commonly found in the lower intestine of warm-blooded organisms (endotherms).
- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.
- **molecular cloning**: a set of experimental methods in molecular biology that are used to assemble recombinant DNA molecules and to direct their replication within host organisms.

A very large number of host organisms and molecular cloning vectors are in use, but the great majority of molecular cloning experiments begin with a laboratory strain of the bacterium *E. coli* (*Escherichia coli*) and a plasmid cloning vector. *E. coli* and plasmid vectors are in common use because they are technically sophisticated, versatile, widely available, and offer rapid growth of recombinant organisms with minimal equipment. If the DNA to be cloned is exceptionally large (hundreds of thousands to millions of base pairs), then a bacterial artificial chromosome or yeast artificial chromosome vector is often chosen.

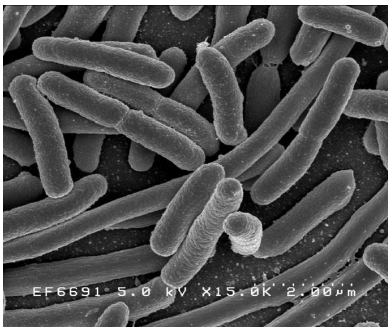

Figure: **Classification of E. coli**: Domain: Bacteria, Kingdom: Eubacteria, Phylum: Proteobacteria, Class: Gammaproteobacteria, Order: Enterobacteriales, Family: Enterobacteriaceae, Genus: Escherichia, Species: E. coli.

Specialized applications may call for specialized host-vector systems. For example, if the experimentalists wish to harvest a particular protein from the recombinant organism, then an expression vector is chosen that contains appropriate signals for transcription and translation in the desired host organism. Alternatively, if replication of the DNA in different species is desired (for example transfer of DNA from bacteria to plants), then a multiple host range vector (also termed shuttle vector) may be selected. In practice, however, specialized molecular cloning experiments usually begin with cloning into a bacterial plasmid, followed by subcloning into a specialized vector.

Whatever combination of host and vector are used, the vector almost always contains four DNA segments that are critically important to its function and experimental utility–(1) an origin of DNA replication is necessary for the vector (and recombinant sequences linked to it) to replicate inside the host organism, (2) one or more unique restriction endonuclease recognition sites that serves as sites where foreign DNA may be introduced, (3) a selectable genetic marker gene that can be used to enable the survival of cells that have taken up vector sequences, and (4) an additional gene that can be used for screening which cells contain foreign DNA.

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7.14D: Shuttle Vectors and Expression Vectors

An expression vector is generally a plasmid that is used to introduce a specific gene into a target cell.

LEARNING OBJECTIVES

Explain the structure and function of shuttle and expression vectors

Key Takeaways

Key Points

- The plasmid is frequently engineered to contain regulatory sequences that act as enhancer and promoter regions and lead to efficient transcription of the gene carried on the expression vector.
- Expression vectors must have expression signals such as a strong promoter, a strong termination codon, adjustment of the distance between the promoter and the cloned gene, and the insertion of a transcription termination sequence and a portable translation initiation sequence.
- Expression vectors are used for molecular biology techniques such as site-directed mutagenesis.

Key Terms

- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.
- **expression vector**: An expression vector, otherwise known as an expression construct, is generally a plasmid that is used to introduce a specific gene into a target cell.
- **transcription**: The synthesis of RNA under the direction of DNA.

An expression vector, otherwise known as an expression construct, is generally a plasmid that is used to introduce a specific gene into a target cell. Once the expression vector is inside the cell, the protein that is encoded by the gene is produced by the cellular-transcription and translation machinery ribosomal complexes. The plasmid is frequently engineered to contain regulatory sequences that act as enhancer and promoter regions and lead to efficient transcription of the gene carried on the expression vector. The goal of a well-designed expression vector is the production of large amounts of stable messenger RNA, and in extension, proteins. Expression vectors are basic tools for biotechnology and the production of proteins such as insulin, which is important for the treatment of diabetes.

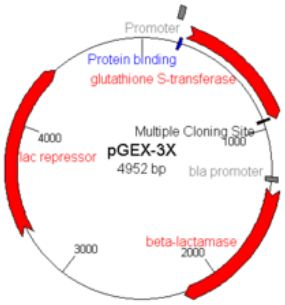

Figure: **The pGEX-3x Plasmid**: The pGEX-3x plasmid is a popular cloning vector. Please note the presence of a multiple cloning site, a promoter, a repressor, and a selectable marker.

After expression of the gene product, the purification of the protein is required; but since the vector is introduced to a host cell, the protein of interest should be purified from the proteins of the host cell. Therefore, to make the purification process easy, the cloned gene should have a tag. This tag could be histidine (His) tag or any other marker peptide.

Expression vectors are used for molecular biology techniques such as site-directed mutagenesis. Cloning vectors, which are very similar to expression vectors, involve the same process of introducing a new gene into a plasmid, but the plasmid is then added into bacteria for replication purposes. In general, DNA vectors that are used in many molecular-biology gene-cloning experiments need not result in the expression of a protein.

Expression vectors must have expression signals such as a strong promoter, a strong termination codon, adjustment of the distance between the promoter and the cloned gene, and the insertion of a transcription termination sequence and a PTIS (portable translation initiation sequence).

A shuttle vector is a vector that can propagate in two different host species, hence, inserted DNA can be tested or manipulated in two different cell types. The main advantage of these vectors is that they can be manipulated in E. coli and then used in a system which is more difficult or slower to use.

Shuttle vectors can be used in both eukaryotes and prokaryotes. Shuttle vectors are frequently used to quickly make multiple copies of the gene in E. coli (amplification). They can also be used for in vitro experiments and modifications such as mutagenesis and PCR. One of the most common types of shuttle vectors is the yeast shuttle vector that contains components allowing for the replication and selection in both E. coli cells and yeast cells. The E. coli component of a yeast shuttle vector includes an origin of replication and a selectable marker, such as an antibiotic resistance like beta lactamase. The yeast component of a yeast shuttle vector includes an autonomously replicating sequence (ARS), a yeast centromere (CEN), and a yeast selectable marker.

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7.14E: Bacteriophage Lambda as a Cloning Vector

Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus that infects the bacterial species Escherichia coli.

LEARNING OBJECTIVES

Describe the life cycle of lambda phage

Key Takeaways

Key Points

- Lambda phage consists of a virus particle including a head (also known as a capsid), tail and tail fibers.
- Specialized transduction is the process by which a restricted set of bacterial genes are transferred to another bacterium.
- The genes that get transferred (donor genes) depend on where the phage genome is located on the chromosome.

Key Terms

- **transduction**: Transduction is the process by which DNA is transferred from one bacterium to another by a virus.
- **lysogeny**: the process by which a bacteriophage incorporates its nucleic acids into a host bacterium
- **Lambda phage**: Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species Escherichia coli. This virus is temperate and may reside within the genome of its host through lysogeny.

Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species Escherichia coli. This virus is temperate and may reside within the genome of its host through lysogeny.

Lambda phage consists of a virus particle including a head (also known as a capsid), tail and tail fibers. The head contains the phage's double-stranded circular DNA genome. The phage particle recognizes and binds to its host, E. coli, causing DNA in the head of the phage to be ejected through the tail into the cytoplasm of the bacterial cell. Usually, a "lytic cycle" ensues, where the lambda DNA is replicated many times and the genes for head, tail and lysis proteins are expressed. This leads to assembly of multiple new phage particles within the cell and subsequent cell lysis, releasing the cell contents, including virions that have been assembled, into the environment. However, under certain conditions, the phage DNA may integrate itself into the host cell chromosome in the lysogenic pathway. In this state, the λ DNA is called a prophage and stays resident within the host's genome without apparent harm to the host. The host can be termed a lysogen when a prophage is present.

Lambda phage has been of major importance in the study of specialized transduction.

Specialized transduction is the process by which a restricted set of bacterial genes are transferred to another bacterium. The genes that get transferred (donor genes) depend on where the phage genome is located on the chromosome. Specialized transduction occurs when the prophage excises imprecisely from the chromosome so that bacterial genes lying adjacent to the prophage are included in the excised DNA. The excised DNA is then packaged into a new virus particle, which delivers the DNA to a new bacterium where the donor genes can be inserted into the recipient chromosome or remain in the cytoplasm, depending on the nature of the bacteriophage. When the partially encapsulated phage material infects another cell and becomes a "prophage" (is covalently bonded into the infected cell's chromosome), the partially coded prophage DNA is called a "heterogenote. "

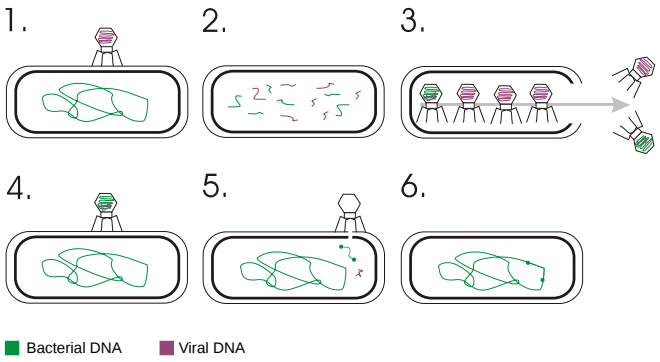

Figure: **Transduction**: Transduction is the process by which DNA is transferred from one bacterium to another by a virus.It also refers to the process whereby foreign DNA is introduced into another cell via a viral vector.

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7.14F: Vectors for Genomic Cloning and Sequencing

In molecular biology, a vector is a DNA molecule used as a vehicle to transfer foreign genetic material into another cell.

LEARNING OBJECTIVES

Differentiate between expression vectors and transcription vectors

Key Takeaways

Key Points

- The vector itself is generally a DNA sequence that consists of an insert (transgene) and a larger sequence that serves as the "backbone" of the vector.
- The four major types of vectors are plasmids, viral vectors, cosmids, and artificial chromosomes.
- Common to all engineered vectors are an origin of replication, a multicloning site, and a selectable marker.

Key Terms

- **vector**: A carrier of a disease-causing agent.
- **plasmids**: Plasmids are double-stranded generally circular DNA sequences that are capable of automatically replicating in a host cell.
- **chromosomes**: A chromosome is an organized structure of DNA and protein found in cells. It is a single piece of coiled DNA containing many genes, regulatory elements, and other nucleotide sequences.

In molecular biology, a vector is a DNA molecule used as a vehicle to transfer foreign genetic material into another cell. The four major types of vectors are plasmids, viral vectors, cosmids, and artificial chromosomes. Common to all engineered vectors are an origin of replication, a multicloning site, and a selectable marker.

The vector itself is generally a DNA sequence that consists of an insert (transgene) and a larger sequence that serves as the "backbone" of the vector. The purpose of a vector which transfers genetic information to another cell is typically to isolate, multiply, or express the insert in the target cell. Vectors called expression vectors (expression constructs) are specifically for the expression of the transgene in the target cell, and generally have a promoter sequence that drives expression of the transgene. Simpler vectors called transcription vectors are only capable of being transcribed but not translated: they can be replicated in a target cell but not expressed, unlike expression vectors. Transcription vectors are used to amplify their insert.

Insertion of a vector into the target cell is usually called transformation for bacterial cells, and transfection for eukaryotic cells, although the insertion of a viral vector is often called transduction.

Plasmids are double-stranded generally circular DNA sequences that are capable of automatically replicating in a host cell. Plasmid vectors minimalistically consist of an origin of replication that allows for semi-independent replication of the plasmid in the host and also the transgene insert. Modern plasmids generally have many more features, notably including a "multiple cloning site" which includes nucleotide overhangs for insertion of an insert, and multiple restriction enzyme consensus sites to either side of the insert.

In the case of plasmids utilized as transcription vectors, incubating bacteria with plasmids generates hundreds or thousands of copies of the vector within the bacteria in hours. The vectors can be extracted from the bacteria, and the multiple cloning sites can be cut by restriction enzymes to excise the hundredfold or thousandfold amplified insert. These plasmid transcription vectors characteristically lack crucial sequences that code for polyadenylation sequences and translation termination sequences in translated mRNAs, making protein expression from transcription vectors impossible.

Plasmids may be conjugative / transmissible and non-conjugative. Conjugative vectors mediate DNA transfer through conjugation and therefore spread rapidly among the bacterial cells of a population, such as the F plasmid, as well as many R and some col plasmids. Non-conjugative vectors do not mediate DNA through conjugation, such as many R and col plasmids.

Viral vectors are generally genetically-engineered viruses carrying modified viral DNA or RNA that has been rendered noninfectious, but still contain viral promoters and also the transgene. This allows for the translation of the transgene through a viral promoter. However, because viral vectors are frequently lacking infectious sequences, they require helper viruses or packaging lines for large-scale transfection. Viral vectors are often designed for permanent incorporation of the insert into the host genome, and thus leave distinct genetic markers in the host genome after incorporating the transgene. For example, retroviruses

leave a characteristic retroviral integration pattern after insertion that is detectable and indicates that the viral vector has incorporated into the host genome.

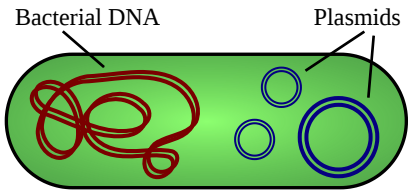

Figure: **A Plasmid**

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SECTION OVERVIEW

7.15: Genome Evolution

Topic hierarchy

7.15A: Gene Families

7.15B: Genomics and Biofuels

7.15C: Genome Reduction

7.15D: Pathogenicity Islands

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7.15A: Gene Families

Gene families are groups of functionally related genes arising from a duplicated gene.

LEARNING OBJECTIVES

Distinguish gene families from gene complexes

Key Takeaways

Key Points

- Genes duplicate over evolutionary times. As they duplicate this can lead to families of related genes. Since they come from the same progenitor gene, they often have related biochemical functions.
- Gene families can expand and contract over evolutionary time scales.
- Gene complexes are groups of genes that work in a fashion similar to gene families; however, they need not arise from gene duplication.

Key Terms

- **phylogenetic**: Of or relating to the evolutionary development of organisms.
- **secondary structure**: The general three-dimensional structure of a biopolymer such as DNA or a protein.

A gene family is a set of several similar genes, formed by duplication of a single original gene, that generally have similar biochemical functions. One such family are the genes for human haemoglobin subunits. The 10 genes are in two clusters on different chromosomes, called the α-globin and β-globin loci. Genes are categorized into families based on shared nucleotide or protein sequences. Phylogenetic techniques can be used as a more rigorous test. The positions of exons within the coding sequence can be used to infer common ancestry. Knowing the sequence of the protein encoded by a gene can allow researchers to apply methods that find similarities among protein sequences that provide more information than similarities or differences among DNA sequences. Furthermore, knowledge of the protein's secondary structure gives further information about ancestry, since the organization of secondary structural elements presumably would be conserved even if the amino acid sequence changes considerably.

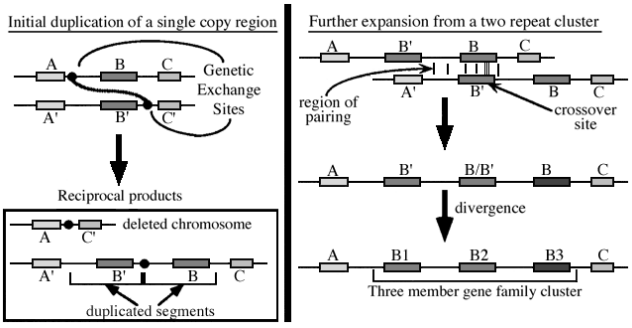

Figure: **Evolution of a Gene Family**: Unequal crossing over generates gene families. The left side illustrates an unequal crossing over event and the two products that are generated. One product is deleted and the other is duplicated for the same region. In this example, the duplicated region contains a second complete copy of a single gene (B). The right side illustrates a second round of unequal crossing over that can occur in a genome that is homozygous of the original duplicated chromosome. In this case, the crossover event has occurred between the two copies of the original gene. Only the duplicated product generated by this event is shown. Over time, the three copies of the B gene can diverge into three distinct functional units (B1, B2, and B3) of a gene family cluster.

These methods often rely upon predictions based upon the DNA sequence. If the genes of a gene family encode proteins, the term protein family is often used in an analogous manner to gene family. The expansion or contraction of gene families along a specific lineage can be due to chance or can be the result of natural selection. To distinguish between these two cases is often difficult in practice. Recent work uses a combination of statistical models and algorithmic techniques to detect gene families that are under the effect of natural selection.

In contrast, gene complexes are simply tightly linked groups of genes, often created via gene duplication (sometimes called segmental duplication if the duplicates remain side-by-side). Here, each gene has a similar though slightly diverged function.

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7.15B: Genomics and Biofuels

Learning Objectives

- Explain the process of creating new biofuels by using microbial genomics

Knowledge of the genomics of microorganisms is being used to find better ways to harness biofuels from algae and cyanobacteria. The primary sources of fuel today are coal, oil, wood, and other plant products, such as ethanol. Although plants are renewable resources, there is still a need to find more alternative renewable sources of energy to meet our population ‘s energy demands. The microbial world is one of the largest resources for genes that encode new enzymes and produce new organic compounds, and it remains largely untapped.

For microbial biomass breakdown, many candidates have already been identified. These include Clostridia species for their ability to degrade cellulose, and fungi that express genes associated with the decomposition of the most recalcitrant features of the plant cell wall, lignin, the phenolic “glue” that imbues the plant with structural integrity and pest resistance. The white rot fungus *Phanerochaete chrysosporium* produces unique extracellular oxidative enzymes that effectively degrade lignin by gaining access through the protective matrix surrounding the cellulose microfibrils of plant cell walls.

Another fungus, the yeast *Pichia stipitis*, ferments the five-carbon “wood sugar” xylose abundant in hardwoods and agricultural harvest residue. *Pichia*‘s recently-sequenced genome has revealed insights into the metabolic pathways responsible for this process, guiding efforts to optimize this capability in commercial production strains. Pathway engineering promises to produce a wider variety of organisms able to ferment the full repertoire of sugars derived from cellulose and hemicellulose and tolerate higher ethanol concentrations to optimize fuel yields. For instance, the hindgut contents of nature’s own bioreactor, the termite, has yielded more than 500 genes related to the enzymatic deconstruction of cellulose and hemicellulose.



Figure: ***Termites: Nature’s Bioreactors****: The hindgut of the termite has yielded more than 500 genes of microbes related to the enzymatic deconstruction of cellulose.*

Key Points

- Microorganisms can encode new enzymes and produce new organic compounds that can be used as biofuels.
- Genomic analysis of the fungus *Pichia* will allow optimization of its use in fermenting ethanol fuels.
- Analysis of the microbes in the hindgut of termites have found 500 genes that may be useful in enzymatic destruction of cellulose.
- Genetic markers have been used in forensic analysis, like in 2001 when the FBI used microbial genomics to determine a specific strain of anthrax that was found in several pieces of mail.
- Genomics is used in agriculture to develop plants with more desirable traits, such as drought and disease resistance.

Key Terms

- **renewable resource**: a natural resource such that it is replenished by natural processes at a rate comparable to its rate of consumption by humans or other users
- **biofuel**: any fuel that is obtained from a renewable biological resource

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7.15C: Genome Reduction

Learning Objectives

- Review genome reduction

Genome size is the total amount of DNA contained within one copy of a single genome. Over evolutionary times, genomes tend to increase in size due to the accumulation of duplication of the genome and an increase in genetic elements. The opposite or genome reduction also occurs. Genome reduction, also known as genome degradation, is the process by which a genome shrinks relative to its ancestor. Genomes fluctuate in size regularly; however, genome size reduction is most significant in bacteria.The most evolutionary significant cases of genome reduction may be the eukaryotic organelles that are derived from bacteria: the mitochondrion and plastid. These organelles are descended from endosymbionts, which can only survive within the host cell and which the host cell likewise needs for survival. Many mitochondria have less than 20 genes in their entire genome, whereas a free-living bacterium generally has at least 1000 genes. Many genes have been transferred to the host nucleus, while others have simply been lost and their function replaced by host processes.Other bacteria have become endosymbionts or obligate intracellular pathogens and have experienced extensive genome reduction as a result. This process seems to be dominated by genetic drift resulting from small population size, low recombination rates, and high mutation rates, as opposed to selection for smaller genomes. Some free-living marine bacterioplanktons also shows signs of genome reduction, which are hypothesized to be driven by natural selection.

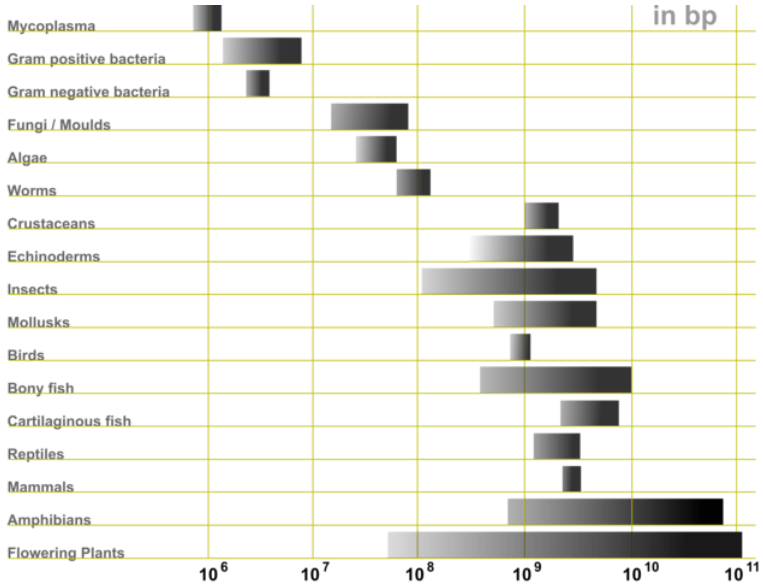

Figure: ***Variation in genome sizes****: A graph show the relative size of genomes, generally more "complex" organisms have larger genomes.*

Obligate endosymbiotic species are characterized by a complete inability to survive outside their host environment. These species have become a considerable threat to human health, as they are often highly capable of evading human immune systems and manipulating the host environment to acquire nutrients. A common explanation for these keen manipulative abilities is the compact and efficient genomic structure consistently found in obligate endosymbionts. This compact genome structure is the result of massive losses of extraneous DNA – an occurrence that is exclusively associated with the loss of a free-living stage. In fact, as much as 90% of the genetic material can be lost when a species makes the evolutionary transition from a free-living to obligate intracellular lifestyle. Common examples of species with reduced genomes include: *Buchnera aphidicola*, *Rickettsia prowazekii* and *Mycobacterium leprae*. One obligate endosymbiont of psyllid, *Candidatus Carsonella ruddii*, has the smallest genome currently known among cellular organisms at 160kb. It is important to note, however, that some obligate intracellular species have positive fitness effects on their hosts. The reductive evolution model has been proposed as an effort to define the genomic commonalities seen in all obligate endosymbionts. This model illustrates four general features of reduced genomes and obligate intracellular species: 'genome streamlining' resulting from relaxed selection on genes that are superfluous in the intracellular environment; a bias towards deletions (rather than insertions), which heavily affects genes that have been disrupted by accumulation of mutations (pseudogenes); very little or no capability for acquiring new DNA; and considerable reduction of

effective population size in endosymbiotic populations, particularly in species that rely on vertical transmission. Based on this model, it is clear that endosymbionts face different adaptive challenges than free-living species.

Key Points

- Genomes tend to increase in size over time, however exceptions occur.
- Genome reduction is observed in species that depend on a host for survival, the most extreme examples are eukaryotic organelles that have bacterial origins such as mitochondria.
- As an endosymbiont becomes dependent on its host, it becomes an obligate endosymbiont; during this time the genome is reduced due to deletions of genes not needed to live in the host. Parts of the genome can be transferred to the host as well, leading to further genome reduction.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.
- **endosymbiont**: An organism that lives within the body or cells of another organism.

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7.15D: Pathogenicity Islands

Learning Objectives

- Describe pathogenicity islands

Pathogenicity islands (PAIs) are a distinct class of genomic islands acquired by microorganisms through horizontal gene transfer. They are incorporated in the genome of pathogenic organisms, but are usually absent from those nonpathogenic organisms of the same or closely related species. These mobile genetic elements may range from 10-200 kb and encode genes which contribute to the virulence of the respective pathogen. Typical examples are adherence factors, toxins, iron uptake systems, invasion factors, and secretion systems. Pathogenicity islands are discrete genetic units flanked by direct repeats, insertion sequences or tRNA genes, which act as sites for recombination into the DNA. Cryptic mobility genes may also be present, indicating the provenance as transduction. One species of bacteria may have more than one PAI (i.e. Salmonella has at least 5). They are transferred through horizontal gene transfer events such as transfer by a plasmid, phage, or conjugative transposon.

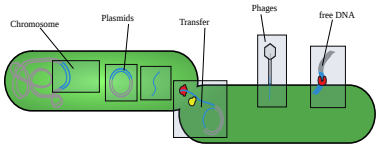

Figure: **Horizontal Transfer**: Pathogenicity islands are transferred horizontally, this details some of the ways that occurs.

Pathogenicity islands carry genes encoding one or more virulence factors, including, but not limited to, adhesins, toxins, or invasins. They may be located on a bacterial chromosome or may be transferred within a plasmid. The GC-content of pathogenicity islands often differs from that of the rest of the genome, potentially aiding in their detection within a given DNA sequence. PAIs are flanked by direct repeats; the sequence of bases at two ends of the inserted sequence is the same. They carry functional genes, such as integrases, transposases, or part of insertion sequences, to enable insertion into host DNA. PAIs are often associated with tRNA genes, which target sites for this integration event. They can be transferred as a single unit to new bacterial cells, thus conferring virulence to formerly benign strains.

Key Points

- A host may have more than one pathogenicity island.
- Pathogenicity islands are transferred horizontally, through plasmids or transposons.
- The addition of a pathogenicity island to a non-invasive species can make the non-invasive species pathogenic.

Key Terms

- **horizontal gene transfer**: The transfer of genetic material from one organism to another one that is not its offspring; especially common among bacteria.
- **transposon**: A segment of DNA that can move to a different position within a genome.
- **integrase**: Any enzyme that integrates viral DNA into that of an infected cell.

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SECTION OVERVIEW

7.16: Environmental Genomics

Topic hierarchy

7.16A: Detecting Uncultured Microorganisms

7.16B: Viral Genomes in Nature

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7.16A: Detecting Uncultured Microorganisms

Using metagenomics, the microbial constituents of the world can be identified by culturing each individual species.

LEARNING OBJECTIVES

Recognize the methods used to detect uncultured microorganisms

Key Takeaways

Key Points

- Many organisms that can cause diseases are not culturable, so a unicellular culture cannot be obtained.
- Initial studies of microbial fauna showed that they are more diverse than expected and contained many microbes that were not culturable.
- Advances in molecular biological techniques allow the sequencing of all or at least many of the genomes of microbes found in a sample.

Key Terms

- **shotgun sequencing**: A DNA sequencing technique in which a large number of small fragments of a long DNA strand are generated at random, sequenced, and reassembled to form a sequence of the original strand.
- **culturable**: Able to be cultured (grown in a suitable environment).
- **high-throughput sequencing**: Technologies that parallelize the sequencing process, producing thousands or millions of sequences at once.

Identification of bacteria in the laboratory is particularly relevant in medicine, where the correct treatment is determined by the bacterial species causing an infection. Consequently, the need to identify human pathogens was a major impetus for the development of techniques to identify bacteria.

Early studies have shown that the microbial life around us in the air, sea, and soil is very diverse and only a small fraction of the species are known. One limitation of identifying human pathogens or conventional sequencing begins with a culture of identical cells as a source of DNA. However, early metagenomic studies revealed that there are probably large groups of microorganisms in many environments that cannot be cultured and thus cannot be sequenced. These early studies focused on 16S ribosomal RNA sequences which are relatively short, often conserved within a species, and generally different between species. Many 16S rRNA sequences have been found which do not belong to any known cultured species, indicating that there are numerous non-isolated organisms out there. These surveys of ribosomal RNA (rRNA) genes taken directly from the environment revealed that cultivation based methods find less than 1% of the bacterial and archaeal species in a sample.

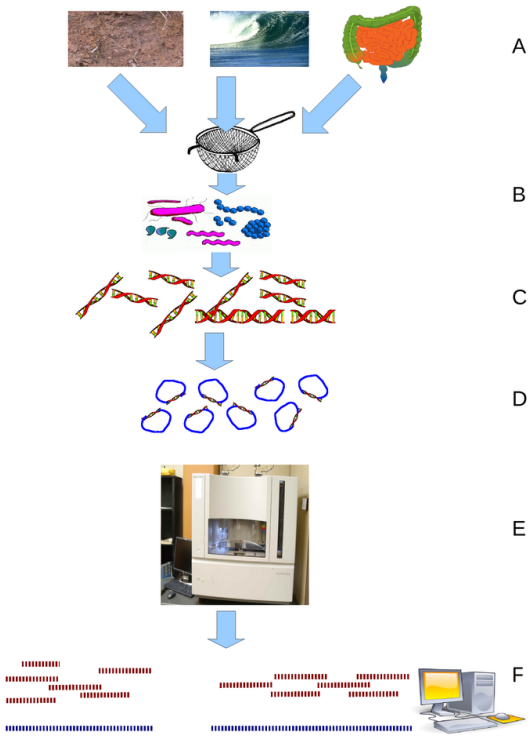

Figure: **Environmental Shotgun Sequencing (ESS)**: (A) sampling from habitat; (B) filtering particles, typically by size; (C) Lysis and DNA extraction; (D) cloning and library construction; (E) sequencing the clones; (F) sequence assembly into contigs and scaffolds

The discovery of such diversity led to the field of metagenomics, which is the study of metagenomes, genetic material recovered directly from environmental samples. Rather than culturing a microbe, this approach takes a sample and identifies the different species in it by sequencing all the species simultaneously. However, recovery of DNA sequences longer than a few thousand base pairs from environmental samples was very difficult until recent advances in molecular biological techniques. More specifically, the construction of libraries in bacterial artificial chromosomes (BACs) provided better vectors for molecular cloning.

Advances in bioinformatics, refinements of DNA amplification, and the proliferation of computational power have greatly aided the analysis of DNA sequences recovered from environmental samples. These advances have allowed the adaptation of shotgun sequencing to metagenomic samples. The approach, used to sequence many cultured microorganisms and the human genome, randomly shears DNA, sequences many short sequences, and reconstructs them into a consensus sequence.

Shotgun sequencing and screens of clone libraries reveal genes present in environmental samples. This can be helpful in understanding the ecology of a community, particularly if multiple samples are compared to each other. This was further followed by high-throughput sequencing which did the same process as the shotgun sequencing but at a much bigger scale in terms of the amount of DNA that could sequenced from one sample. This provides information both on which organisms are present and what metabolic processes are possible in the community. Using metagenomics, and the resultant sequencing of uncultured microbes, metagenomics has the potential to advance knowledge in a wide variety of fields. It can also be applied to solve practical challenges in medicine, engineering, agriculture, and sustainability.

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7.16B: Viral Genomes in Nature

Viruses are the most abundant biological entity on earth, they outnumber all other lifeforms on earth combined.

LEARNING OBJECTIVES

Recognize viral genomic diversity in nature

Key Takeaways

Key Points

- Viruses infect all types of cellular life including animals, plants, bacteria, and fungi.
- Metagenomic sequencing has identified that there are an enormous number of species of virus in nature, showing that a a teaspoon of water has a million species of viruses.
- Viruses kill about 20% of the microbes that constitute the oceans microbial fauna, each day. This viral-driven biological turn over is needed for for life on earth to continue.
- Viruses can transfer genetic material from one species to another, and as such viruses may be a main driving force of evolution.

Key Terms

- **metagenomics**: The study of genomes recovered from environmental samples; especially the differentiation of genomes from multiple organisms or individuals, either in a symbiotic relationship, or at a crime scene.
- **stool**: Feces; excrement.

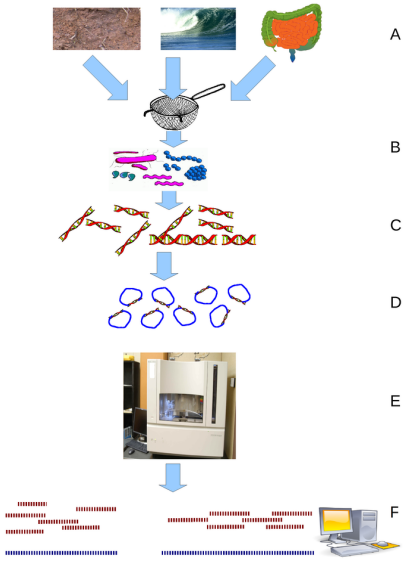

Figure: **Environmental Shotgun Sequencing (ESS)**: (A) sampling from habitat; (B) filtering particles, typically by size; (C) Lysis and DNA extraction; (D) cloning and library construction; (E) sequencing the clones; (F) sequence assembly into contigs and scaffolds

Viruses are by far the most abundant biological entities on earth and they outnumber all the others put together. They infect all types of cellular life including animals, plants, bacteria, and fungi. However, different types of viruses can infect only a limited range of hosts and many are species-specific. Some, such as smallpox virus for example, can infect only one species – in this case humans, and are said to have a narrow host range. Other viruses, such as rabies virus, can infect different species of mammals and are said to have a broad range. The viruses that infect plants are harmless to animals, and most viruses that infect other animals are harmless to humans. The host range of some bacteriophages is limited to a single strain of bacteria and they can be used to trace the source of outbreaks of infections by a method called phage typing.

Metagenomic sequencing is particularly useful in the study of viral communities. As viruses lack a shared universal phylogenetic marker (as 16S RNA for bacteria and archaea, and 18S RNA for eukarya), the only way to access the genetic diversity of the viral community from an environmental sample is through metagenomics. Viral metagenomes (also called viromes) should therefore provide more and more information about viral diversity and evolution. In 2002, Mya Breitbart, Forest Rohwer, and colleagues

used environmental shotgun sequencing to show that 200 liters of seawater contains over 5,000 different viruses. Subsequent studies showed that there are more than a thousand viral species in human stool and possibly a million different viruses per kilogram of marine sediment, including many bacteriophages. Essentially all of the viruses in these studies were new species.

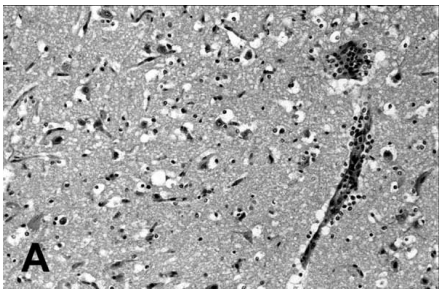

Figure: **Phocine distermper encephalitis**: This is a section from a harbor seal cerebral cortex. The white areas are tissue lesions caused a phocine distermper viral infection.

To understand the complex diversity of viruses a further look at viruses in aquatic environments shows, a teaspoon of seawater contains about one million viruses. They are essential to the regulation of saltwater and freshwater ecosystems. Most of these viruses are bacteriophages, which are harmless to plants and animals. They infect and destroy the bacteria in aquatic microbial communities, comprising the most important mechanism of recycling carbon in the marine environment. The organic molecules released from the bacterial cells by the viruses stimulate fresh bacterial and algal growth. Microorganisms constitute more than 90% of the biomass in the sea. It is estimated that viruses kill approximately 20% of this biomass each day and that there are 15 times as many viruses in the oceans as there are bacteria and archaea. Viruses are the main agents responsible for the rapid destruction of harmful algal blooms, which often kill other marine life. The number of viruses in the oceans decreases further offshore and deeper into the water, where there are fewer host organisms. The effects of marine viruses are far-reaching. By increasing the amount of photosynthesis in the oceans, viruses are indirectly responsible for reducing the amount of carbon dioxide in the atmosphere by approximately three gigatonnes of carbon per year. Like any organism, marine mammals are susceptible to viral infections. In 1988 and 2002, thousands of harbor seals were killed in Europe by phocine distemper virus. Many other viruses, including caliciviruses, herpesviruses, adenoviruses, and parvoviruses circulate in marine mammal populations.

Viruses are an important natural means of transferring genes between different species, which increases genetic diversity and drives evolution. It is thought that viruses played a central role in the early evolution, before the diversification of bacteria, archaea, and eukaryotes and at the time of the last universal common ancestor of life on earth. Viruses are still one of the largest reservoirs of unexplored genetic diversity on earth.

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SECTION OVERVIEW

7.17: Molecular Regulation

Topic hierarchy

7.17A: Catabolite Activator Protein (CAP) - An Activator Regulator

7.17B: The Initiation Complex and Translation Rate

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7.17A: Catabolite Activator Protein (CAP) - An Activator Regulator

Learning Objectives

Explain how an activator works to increase transcription of a gene

Just as the trp operon is negatively regulated by tryptophan molecules, there are proteins that bind to the operator sequences that act as a positive regulator to turn genes on and activate them. For example, when glucose is scarce, *E. coli*bacteria can turn to other sugar sources for fuel. To do this, new genes to process these alternate genes must be transcribed. This type of process can be seen in the lac operon which is turned on in the presence of lactose and absence of glucose.

When glucose levels drop, cyclic AMP (cAMP) begins to accumulate in the cell. The cAMP molecule is a signaling molecule that is involved in glucose and energy metabolism in *E. coli*. When glucose levels decline in the cell, accumulating cAMP binds to the positive regulator catabolite activator protein (CAP), a protein that binds to the promoters of operons that control the processing of alternative sugars, such as the lac operon. The CAP assists in production in the absence of glucose. CAP is a transcriptional activator that exists as a homodimer in solution, with each subunit comprising a ligand-binding domain at the N-terminus, which is also responsible for the dimerization of the protein and a DNA-binding domain at the C-terminus. Two cAMP molecules bind dimeric CAP with negative cooperativity and function as allosteric effectors by increasing the protein's affinity for DNA. CAP has a characteristic helix-turn-helix structure that allows it to bind to successive major grooves on DNA. This opens up the DNA molecule, allowing RNA polymerase to bind and transcribe the genes involved in lactose catabolism. When cAMP binds to CAP, the complex binds to the promoter region of the genes that are needed to use the alternate sugar sources. In these operons, a CAP-binding site is located upstream of the RNA-polymerase-binding site in the promoter. This increases the binding ability of RNA polymerase to the promoter region and the transcription of the genes. As cAMP-CAP is required for transcription of the lac operon, this requirement reflects the greater simplicity with which glucose may be metabolized in comparison to lactose.

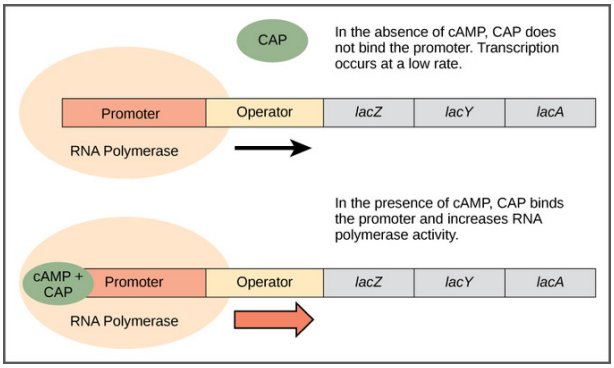

Figure: ***Catabolite Activator Protein (CAP) Regulation****: When glucose levels fall, E. coli may use other sugars for fuel, but must transcribe new genes to do so. As glucose supplies become limited, cAMP levels increase. This cAMP binds to the CAP protein, a positive regulator that binds to an operator region upstream of the genes required to use other sugar sources.*

Key Points

- Catabolite activator protein (CAP) must bind to cAMP to activate transcription of the lac operon by RNA polymerase.
- CAP is a transcriptional activator with a ligand-binding domain at the N-terminus and a DNA -binding domain at the C-terminus.
- cAMP molecules bind to CAP and function as allosteric effectors by increasing CAP's affinity to DNA.

Key Terms

- **RNA polymerase**: a DNA-dependent RNA polymerase, an enzyme, that produces RNA
- **operon**: a unit of genetic material that functions in a coordinated manner by means of an operator, a promoter, and structural genes that are transcribed together
- **promoter**: the section of DNA that controls the initiation of RNA transcription

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7.17B: The Initiation Complex and Translation Rate

The first step of translation is ribosome assembly, which requires initiation factors.

LEARNING OBJECTIVES

Discuss how eukaryotes assemble ribosomes on the mRNA to begin translation

Key Takeaways

Key Points

- The components involved in ribosome assembly are brought together by the help of proteins called initiation factors which bind to the small ribosomal subunit.
- Initiator tRNA is used to locate the start codon AUG (the amino acid methionine) which establishes the reading frame for the mRNA strand.
- GTP carried by eIF2 is the energy source used for loading the initiator tRNA carried by the small ribosomal subunit on the correct start codon in the mRNA.
- GTP carried by eIF5 is the energy source for assembling the large and small ribosomal subunits together.

Key Terms

- **reading frame**: either of three possible triplets of codons in which a DNA sequence could be transcribed
- **phosphorylation**: the addition of a phosphate group to a compound; often catalyzed by enzymes

Ribosome Assembly and Translation Rate

Like transcription, translation is controlled by proteins that bind and initiate the process. In translation, before protein synthesis can begin, ribosome assembly has to be completed. This is a multi-step process.

In ribosome assembly, the large and small ribosomal subunits and an initiator tRNA ($tRNA_i$) containing the first amino acid of the final polypeptide chain all come together at the translation start codon on an mRNA to allow translation to begin. First, the small ribosomal subunit binds to the $tRNA_i$ which carries methionine in eukaryotes and archaea and carries N-formyl-methionine in bacteria. (Because the $tRNA_i$ is carrying an amino acid, it is said to be charged.) Next, the small ribosomal subunit with the charged $tRNA_i$ still bound scans along the mRNA strand until it reaches the start codon AUG, which indicates where translation will begin. The start codon also establishes the reading frame for the mRNA strand, which is crucial to synthesizing the correct sequence of amino acids. A shift in the reading frame results in mistranslation of the mRNA. The anticodon on the $tRNA_i$ then binds to the start codon via basepairing. The complex consisting of mRNA, charged $tRNA_i$, and the small ribosomal subunit attaches to the large ribosomal subunit, which completes ribosome assembly. These components are brought together by the help of proteins called initiation factors which bind to the small ribosomal subunit during initiation and are found in all three domains of life. In addition, the cell spends GTP energy to help form the initiation complex. Once ribosome assembly is complete, the charged $tRNA_i$ is positioned in the P site of the ribosome and the empty A site is ready for the next aminoacyl-tRNA. The polypeptide synthesis begins and always proceeds from the N-terminus to the C-terminus, called the N-to-C direction.

In eukaryotes, several eukaryotic initiation factor proteins (eIFs) assist in ribosome assembly. The eukaryotic initiation factor-2 (eIF-2) is active when it binds to guanosine triphosphate (GTP). With GTP bound to it, eIF-2 protein binds to the small 40S ribosomal subunit. Next, the initiatior tRNA charged with methionine (Met-$tRNA_i$) associates with the GTP-eIF-2/40S ribosome complex, and once all these components are bound to each other, they are collectively called the 43S complex.

Eukaryotic initiation factors eIF1, eIF3, eIF4, and eIF5 help bring the 43S complex to the 5′-m^7G cap of an mRNA be translated. Once bound to the mRNA's 5′ m^7G cap, the 43S complex starts travelling down the mRNA until it reaches the initiation AUG codon at the start of the mRNA's reading frame. Sequences around the AUG may help ensure the correct AUG is used as the initiation codon in the mRNA.

Once the 43S complex is at the initiation AUG, the tRNAi-Met is positioned over the AUG. The anticodon on $tRNA_i$-Met basepairs with the AUG codon. At this point, the GTP bound to eIF2 in the 43S complexx is hydrolyzed to GDP + phosphate, and energy is released. This energy is used to release the eIF2 (with GDP bound to it) from the 43S complex, leaving the 40S ribosomal subunit and the $tRNA_i$-Met at the translation start site of the mRNA.

Next, eIF5 with GTP bound binds to the 40S ribosomal subunit complexed to the mRNA and the $tRNA_i$-Met. The eIF5-GTP allows the 60S large ribosomal subunit to bind. Once the 60S ribosomal subunit arrives, eIF5 hydrolyzes its bound GTP to GDP + phosphate, and energy is released. This energy powers assembly of the two ribosomal subunits into the intact 80S ribosome, with tRNAi-Met in its P site while also basepaired to the initiation AUG codon on the mRNA. Translation is ready to begin.

The binding of eIF-2 to the 40S ribosomal subunit is controlled by phosphorylation. If eIF-2 is phosphorylated, it undergoes a conformational change and cannot bind to GTP. Therefore, the 43S complex cannot form properly and translation is impeded. When eIF-2 remains unphosphorylated, it binds the 40S ribosomal subunit and actively translates the protein.

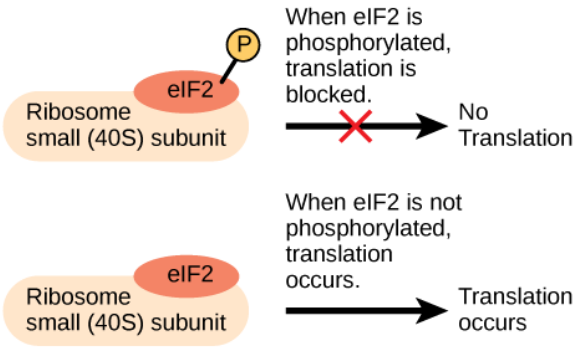

Figure: **Translation Initiation Complex**: Gene expression can be controlled by factors that bind the translation initiation complex.

The ability to fully assemble the ribosome directly affects the rate at which translation occurs. But protein synthesis is regulated at various other levels as well, including mRNA synthesis, tRNA synthesis, rRNA synthesis, and eukaryotic initiation factor synthesis. Alteration in any of these components affects the rate at which translation can occur.

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SECTION OVERVIEW

7.18: Global Regulatory Mechanisms

Topic hierarchy

7.18A: Transcription in Prokaryotes

7.18B: The trp Operon - A Repressor Operon

7.18C: The Stringent Response

7.18D: Repression of Anabolic Pathways

7.18E: The AraC Regulator

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7.18A: Transcription in Prokaryotes

The genetic code is a degenerate, non-overlapping set of 64 codons that encodes for 21 amino acids and 3 stop codons.

LEARNING OBJECTIVES

Describe the genetic code and how the nucleotide sequence prescribes the amino acid and the protein sequence

Key Takeaways

Key Points

- The relationship between DNA base sequences and the amino acid sequence in proteins is called the genetic code.
- There are 61 codons that encode amino acids and 3 codons that code for chain termination for a total of 64 codons.
- Unlike, eukayrotes, a bacterial chromosome is a covalently-closed circle.
- The DNA double helix must partially unwind for transcription to occur; this unwound region is called a transcription bubble.

Key Terms

- **nucleotide**: the monomer comprising DNA or RNA molecules; consists of a nitrogenous heterocyclic base that can be a purine or pyrimidine, a five-carbon pentose sugar, and a phosphate group
- **amino acid**: Any of 20 naturally occurring α-amino acids (having the amino, and carboxylic acid groups on the same carbon atom), and a variety of side chains, that combine, via peptide bonds, to form proteins.
- **redundancy**: duplication of components, such as amino acid codons, to provide survival of the total system in case of failure of single components

The Genetic Code: Nucleotide sequences prescribe the amino acids

The genetic code is the relationship between DNA base sequences and the amino acid sequence in proteins. Features of the genetic code include:

- Amino acids are encoded by three nucleotides.
- It is non-overlapping.
- It is degenerate.

There are 21 genetically-encoded amino acids universally found in the species from all three domains of life. (There is a 22nd genetically-encooded amino acid, Pyl, but so far it has only been found in a handful of Archaea and Bacteria species.) Yet there are only four different nucleotides in DNA or RNA, so a minimum of three nucleotides are needed to code each of the 21 (or 22) amino acids. The set of three nucleotides that codes for a single amino acid is known as a codon. There are 64 codons in total, 61 that encode amino acids and 3 that code for chain termination. Two of the codons for chain termination can, under certain circumstances, instead code for amino acids.



Genetic Code Table.: A codon is made of three nucleotides. Consequently there are 4^3 (=64) different codons. The 64 codons encode 22 different amino acids and three termination codons, also called stop codons.

Degeneracy is the redundancy of the genetic code. The genetic code has redundancy, but no ambiguity. For example, although codons GAA and GAG both specify glutamic acid (redundancy), neither of them specifies any other amino acid (no ambiguity). The codons encoding one amino acid may differ in any of their three positions. For example, the amino acid glutamic acid is specified by GAA and GAG codons (difference in the third position); the amino acid leucine is specified by UUA, UUG, CUU, CUC, CUA, CUG codons (difference in the first or third position); while the amino acid serine is specified by UCA, UCG, UCC, UCU, AGU, AGC (difference in the first, second or third position). These properties of the genetic code make it more fault-tolerant for point mutations.

Origin of transcription on prokaryotic organisms

Prokaryotes are mostly single-celled organisms that, by definition, lack membrane-bound nuclei and other organelles. The central region of the cell in which prokaryotic DNA resides is called the nucleoid region. Bacterial and Archaeal chromosomes are covalently-closed circles that are not as extensively compacted as eukaryotic chromosomes, but are compacted nonetheless as the

diameter of a typical prokaryotic chromosome is larger than the diameter of a typical prokaryotic cell. Additionally, prokaryotes often have abundant plasmids, which are shorter, circular DNA molecules that may only contain one or a few genes and often carry traits such as antibiotic resistance.

Transcription in prokaryotes (as in eukaryotes) requires the DNA double helix to partially unwind in the region of RNA synthesis. The region of unwinding is called a transcription bubble. Transcription always proceeds from the same DNA strand for each gene, which is called the template strand. The RNA product is complementary to the template strand and is almost identical to the other (non-template) DNA strand, called the sense or coding strand. The only difference is that in RNA all of the T nucleotides are replaced with U nucleotides.

The nucleotide on the DNA template strand that corresponds to the site from which the first 5′ RNA nucleotide is transcribed is called the +1 nucleotide, or the initiation site. Nucleotides preceding, or 5′ to, the template strand initiation site are given negative numbers and are designated upstream. Conversely, nucleotides following, or 3′ to, the template strand initiation site are denoted with "+" numbering and are called downstream nucleotides.

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7.18B: The trp Operon - A Repressor Operon

Learning Objectives

- Explain the relationship between structure and function of an operon and the ways in which repressors regulate gene expression

Bacteria such as *E. coli* need amino acids to survive. Tryptophan is one such amino acid that *E. coli* can ingest from the environment. *E. coli* can also synthesize tryptophan using enzymes that are encoded by five genes. These five genes are next to each other in what is called the tryptophan (trp) operon. If tryptophan is present in the environment, then *E. coli* does not need to synthesize it; the switch controlling the activation of the genes in the trp operon is turned off. However, when tryptophan availability is low, the switch controlling the operon is turned on, transcription is initiated, the genes are expressed, and tryptophan is synthesized.

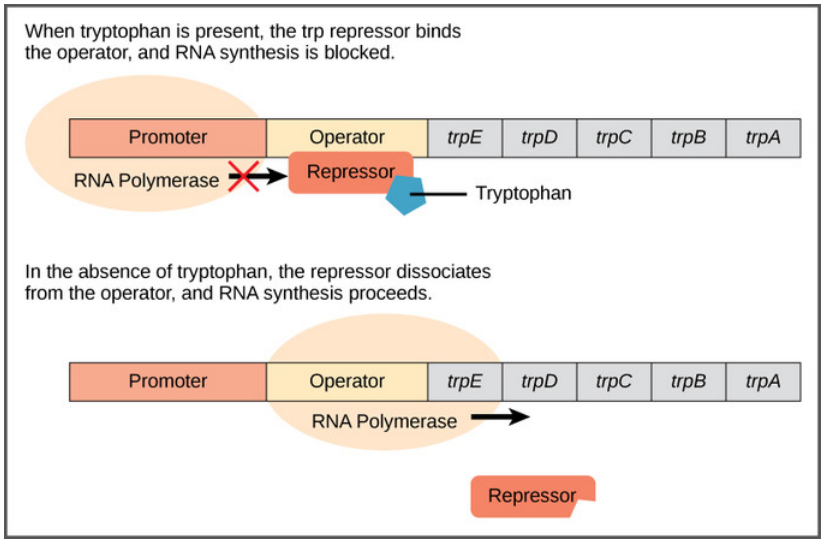

Figure: ***The trp operon****: The five genes that are needed to synthesize tryptophan in E. coli are located next to each other in the trp operon. When tryptophan is plentiful, two tryptophan molecules bind the repressor protein at the operator sequence. This physically blocks the RNA polymerase from transcribing the tryptophan genes. When tryptophan is absent, the repressor protein does not bind to the operator and the genes are transcribed.*

A DNA sequence that codes for proteins is referred to as the coding region. The five coding regions for the tryptophan biosynthesis enzymes are arranged sequentially on the chromosome in the operon. Just before the coding region is the transcriptional start site. This is the region of DNA to which RNA polymerase binds to initiate transcription. The promoter sequence is upstream of the transcriptional start site. Each operon has a sequence within or near the promoter to which proteins (activators or repressors) can bind and regulate transcription.

A DNA sequence called the operator sequence is encoded between the promoter region and the first trp-coding gene. This operator contains the DNA code to which the repressor protein can bind. When tryptophan is present in the cell, two tryptophan molecules bind to the trp repressor, which changes shape to bind to the trp operator. Binding of the tryptophan–repressor complex at the operator physically prevents the RNA polymerase from binding and transcribing the downstream genes.

When tryptophan is not present in the cell, the repressor by itself does not bind to the operator; therefore, the operon is active and tryptophan is synthesized. Because the repressor protein actively binds to the operator to keep the genes turned off, the trp operon is negatively regulated and the proteins that bind to the operator to silence trp expression are negative regulators.

Key Points

- The operator sequence is encoded between the promoter region and the first trp-coding gene.
- The trp operon is repressed when tryptophan levels are high by binding the repressor protein to the operator sequence via a corepressor which blocks RNA polymerase from transcribing the trp-related genes.
- The trp operon is activated when tryptophan levels are low by dissociation of the repressor protein to the operator sequence which allows RNA polymerase to transcribe the trp genes in the operon.

Key Terms

- **repressor**: any protein that binds to DNA and thus regulates the expression of genes by decreasing the rate of transcription
- **operon**: a unit of genetic material that functions in a coordinated manner by means of an operator, a promoter, and structural genes that are transcribed together

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7.18C: The Stringent Response

The stringent response is a stress response that occurs in bacteria in reaction to amino-acid starvation or other stress conditions.

LEARNING OBJECTIVES

Explain the function of the alarmone (p)ppGpp in the stringent response

Key Takeaways

Key Points

- The stringent response is signaled by the alarmone (p)ppGpp.
- In Escherichia coli, (p)ppGpp production is mediated by the ribosomal protein L11 and the ribosome-associated protein RelA.
- In other bacteria, stringent response is mediated by a variety of RelA/SpoT Homologue (RSH) proteins. Some only have synthetic, hydrolytic, or both (Rel) activities.

Key Terms

- **stringent response**: The stringent response, also called stringent control, is a stress response that occurs in bacteria and plant chloroplasts in reaction to amino-acid starvation, fatty acid limitation, iron limitation, heat shock, and other stress conditions.
- **alarmone**: Alarmone is an intracellular signal molecule that is produced due to harsh environmental factors.
- **amino-acid starvation**: The amino acid response pathway is triggered by a shortage of any essential amino acid.

The stringent response, also called stringent control, is a stress response that occurs in bacteria and plant chloroplasts in reaction to amino-acid starvation, fatty acid limitation, iron limitation, heat shock, and other stress conditions. The stringent response is signaled by the alarmone (p)ppGpp and modulating transcription of up to 1/3 of all genes in the cell. This in turn causes the cell to divert resources away from growth and division and toward amino acid synthesis in order to promote survival until nutrient conditions improve.

In *Escherichia coli*, (p)ppGpp production is mediated by the ribosomal protein L11. The ribosome-associated protein RelA with the A-site bound deacylated tRNA is the ultimate inducer. RelA converts GTP and ATP into pppGpp by adding the pyrophosphate from ATP onto the 3′ carbon of the ribose in GTP releasing AMP. pppGpp is converted to ppGpp by the gpp gene product, releasing Pi. ppGpp is converted to GDP by the spoT gene product, releasing pyrophosphate (PPi). GDP is converted to GTP by the ndk gene product. Nucleoside triphosphate (NTP) provides the Pi. It is converted to nucleoside diphosphate (NDP).

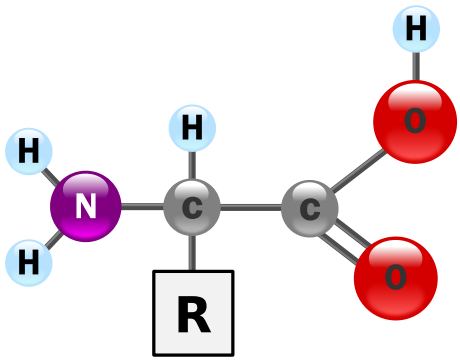

Figure: **An amino acid**: The generic structure of an alpha amino acid in its un-ionized form.

In other bacteria, stringent response is mediated by a variety of RelA/SpoT Homologue (RSH) proteins, with some having only synthetic, hydrolytic, or both (Rel) activities. The disable of stringent response by distruption of relA and spoT in *Pseudomonas aeruginosa*, produces infectious cells and biofilms that have nutrient limitations. They are more susceptible to antibiotics.

During the stringent response, (p)ppGpp accumulation affects the resource-consuming cell processes replication, transcription, and translation. (p)ppGpp is thought to bind RNA polymerase and alter the transcriptional profile, decreasing the synthesis of translational machinery (such as rRNA and tRNA), and increasing the transcription of biosynthetic genes. Additionally, the initiation of new rounds of replication is inhibited and the cell cycle arrests until nutrient conditions improve. Translational GTP involved in protein biosynthesis are also affected by ppGpp, with Initiation Factor 2 (IF2) being the main target.

Chemical reaction catalyzed by RelA: ATP+GTP→AMP+pppGppATP+GTP→AMP+pppGpp

Chemical reaction catalyzed by SpoT: ppGpp→GDP+PPi

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7.18D: Repression of Anabolic Pathways

Repression of anabolic pathways is regulated by altering transcription rates.

LEARNING OBJECTIVES

Differentiate between inducible and repressible systems in gene regulation

Key Takeaways

Key Points

- Regulation of transcription controls when transcription occurs and how much RNA is created.
- Gene regulation is either controlled by an inducible system or a repressible system.
- In prokaryotes, regulation of transcription is needed for the cell to quickly adapt to the ever-changing outer environment.

Key Terms

- **anabolic pathways**: Anabolism describes the set of metabolic pathways that construct molecules from smaller units.
- **transcription**: The synthesis of RNA under the direction of DNA.
- **gene**: A unit of heredity; a segment of DNA or RNA that is transmitted from one generation to the next. It carries genetic information such as the sequence of amino acids for a protein.

Repression of anabolic pathways is regulated by altering transcription rates. Transcriptional regulation is the change in gene expression levels by altering transcription rates.

Regulation of transcription controls when transcription occurs and how much RNA is created. Transcription of a gene by RNA polymerase can be regulated by at least five mechanisms:

- Specificity factors alter the specificity of RNA polymerase for a given promoter or set of promoters, making it more or less likely to bind to them (i.e. sigma factors used in prokaryotic transcription).
- Repressors bind to non-coding sequences on the DNA strand that are close to or overlapping the promoter region, impeding RNA polymerase's progress along the strand, thus impeding the expression of the gene.
- General transcription factors position RNA polymerase at the start of a protein -coding sequence and then release the polymerase to transcribe the mRNA.
- Activators enhance the interaction between RNA polymerase and a particular promoter, encouraging the expression of the gene. Activators do this by increasing the attraction of RNA polymerase for the promoter, through interactions with subunits of the RNA polymerase or indirectly by changing the structure of the DNA.
- Enhancers are sites on the DNA helix that are bound to by activators in order to loop the DNA bringing a specific promoter to the initiation complex.

Regulatory protein is a term used in genetics to describe a protein involved in regulating gene expression. Such proteins are usually bound to a DNA binding site which is sometimes located near the promoter although this is not always the case. Sites of DNA sequences where regulatory proteins bind are called enhancer sequences. Regulatory proteins are often needed to be bound to a regulatory binding site to switch a gene on (activator) or to shut off a gene (repressor). Generally, as the organism grows more sophisticated, its cellular protein regulation becomes more complicated and, indeed, some human genes can be controlled by many activators and repressors working together.

In prokaryotes, regulation of transcription is needed for the cell to quickly adapt to the ever-changing outer environment. The presence or the quantity and type of nutrients determines which genes are expressed; in order to do that, genes must be regulated in some fashion. In prokaryotes, repressors bind to regions called operators that are generally located downstream from and near the promoter (normally part of the transcript). Activators bind to the upstream portion of the promoter, such as the CAP region (completely upstream from the transcript). A combination of activators, repressors and rarely enhancers (in prokaryotes) determines whether a gene is transcribed.

Gene regulation can be summarized as how genes respond: inducible systems or repressible systems. An inducible system is off unless there is the presence of some molecule (called an inducer) that allows for gene expression. The molecule is said to "induce expression. " The manner in which this happens is dependent on the control mechanisms as well as differences between prokaryotic and eukaryotic cells. A repressible system is on except in the presence of some molecule (called a corepressor) that suppresses gene

expression. The molecule is said to “repress expression. ” The manner in which this happens is dependent on the control mechanisms as well as differences between prokaryotic and eukaryotic cells.

For example, when E. coli bacteria are subjected to heat stress, the σ32 subunit of its RNA polymerase changes in such a way that the enzyme binds to a specialized set of promoters that precede genes for heat-shock response proteins.

Another example is when a cell contains a surplus amount of the amino acid tryptophan, the acid binds to a specialized repressor protein (tryptophan repressor). The binding changes the structural conformity of the repressor such that it binds to the operator region for the operon that synthesizes tryptophan, preventing their expression and thus suspending production. This is a form of negative feedback.

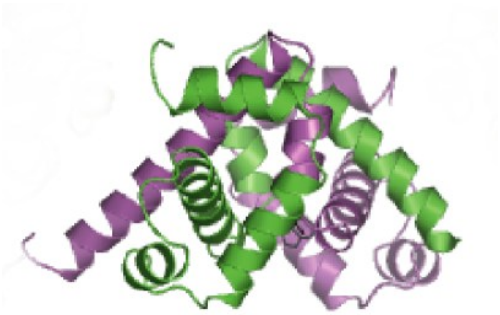

Figure: **Trp Repressor Protein**: Here is a diagram of the Trp repressor protein.

In bacteria, the lac repressor protein blocks the synthesis of enzymes that digest lactose when there is no lactose to feed on. When lactose is present, it binds to the repressor, causing it to detach from the DNA strand.

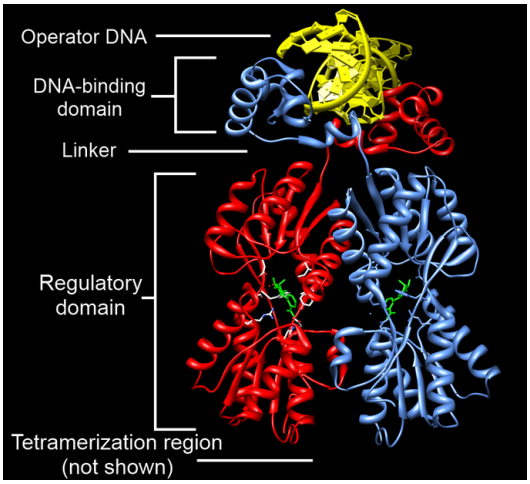

Figure: **Annotated Crystal Structure of Dimeric LacI**: Annotated crystal structure of dimeric LacI. Two monomers (of four total) cooperate to bind each DNA operator sequence. Monomers (red and blue) contain DNA binding and core domains (labeled) which are connected by a linker (labeled). The C-terminal tetramerization helix is not shown. The repressor is shown in complex with operator DNA (gold) and ONPF (green), an anti-inducer ligand (i.e. a stabilizer of DNA binding).

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7.18E: The AraC Regulator

The L-arabinose operon, also called ara operon, encodes enzymes needed for the catabolism of arabinose to xylulose 5-phosphate.

LEARNING OBJECTIVES

Describe the regulatory mechanism of the AraC protein in the presence and absence of arabinose

Key Takeaways

Key Points

- The structural gene, which encodes arabinose breakdown enzymes, is araBAD.
- The ara operon is regulated by the AraC protein.
- When arabinose is present, arabinose binds AraC and prevents it from interacting.

Key Terms

- **operon**: A unit of genetic material that functions in a coordinated manner by means of an operator, a promoter, and structural genes that are transcribed together.
- **L-arabinose**: Arabinose is an aldopentose – a monosaccharide containing five carbon atoms, and including an aldehyde (CHO) functional group.
- **catabolism**: Destructive metabolism, usually includes the release of energy and breakdown of materials.

The L-arabinose operon, also called ara operon, is a gene sequence encoding enzymes needed for the catabolism of arabinose to xylulose 5-phosphate, an intermediate of the pentose phosphate pathway. It has both positive and negative regulation. The operon is found in *Escherichia coli* (*E. coli*).

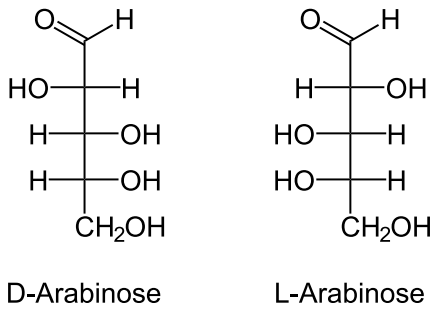

Figure: **Arabinose**: Structure of arabinose.

It has been a focus for research in molecular biology since 1970, and has been investigated extensively at its genetic, biochemical, physiological, and biophysical levels.

The structural gene, which encodes arabinose breakdown enzymes, is araBAD. The regulator gene is araC. The genes, araBAD and araC, are transcribed in opposite directions.

The operators are araI and araO2. The operators lie between the AraC.

AraI lies between the structural genes and the operator. The araI1 and araI2 are DNA -binding sites that, when occupied by AraC, induce expression.

Sequence of the Operon: 5′—araC—araO—araI—araB—araA—araD—3′

The ara operon is regulated by the AraC protein. If arabinose is absent, the dimer AraC protein represses the structural gene by binding to araI1 and araO2 and the DNA forms a loop, which prevents RNA polymerase from binding to the promoter of the ara operon, thereby blocking transcription.

When arabinose is present, arabinose binds AraC and prevents it from interacting. This breaks the DNA loop. The two AraC-arabinose complexes bind to the araI site which promotes transcription. When arabinose is present, AraC acts as an activator and it builds a complex: AraC + arabinose. This complex is needed for RNA polymerase to bind to the promoter and transcribe the *ara*operon.

Also for activation, the binding of another structure to *araI* is needed: CRP (formerly known as CAP) + cyclic AMP. Thus the activation depends on the presence of arabinose and cAMP.

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SECTION OVERVIEW

7.19: RNA-Based Regulation

Topic hierarchy

7.19A: RNA Regulation and Antisense RNA

7.19B: Attenuation

7.19C: Riboswitches

7.19D: Regulation of Sigma Factor Activity

7.19E: Regulation of Sigma Factor Translation

7.19F: Proteolytic Degradation

7.19G: Small Regulatory RNAs

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7.19A: RNA Regulation and Antisense RNA

Antisense RNAs are single-stranded RNA molecules that can bind and inhibit specific mRNA translation to protein.

Learning Objectives

- Explain RNA regulation via antisense RNA

Key Points

- Antisense RNAs are specific to mRNAs based on the principle of complementary base pairs.
- Antisense RNAs bind to mRNAs and inhibit the ability of these mRNAs to be translated into functioning protein.
- Naturally occurring antisense RNAs have been identified in E. coli, which carry an R1 plasmid and control the hok/sok system that involves the production of toxic and antitoxic products.

Key Terms

- **morphogenesis**: The differentiation of tissues and growth in organisms.

Gene regulation, the ability to control whether a gene is expressed or not, is critical in controlling cellular and metabolic processes and contributes to diversity and variation in organisms. Furthermore, it is the key determinant in cellular differentiation and morphogenesis. There are specific types of RNA molecules that can be utilized to control gene regulation, including messenger RNAs (mRNAs), small RNAs such as microRNAs and lastly, antisense RNAs. The following is a brief overview of antisense RNAs and their role in RNA regulation. Antisense RNAs have been recently investigated as a new class of antiviral drugs.

Antisense RNAs are single-stranded RNA molecules that exhibit a complementary relationship to specific mRNAs. Antisense RNAs are utilized for gene regulation and specifically target mRNA molecules that are used for protein synthesis. The antisense RNA can physically pair and bind to the complementary mRNA, thus inhibiting the ability of the mRNA to be processed in the translation machinery. Pairing antisense RNA is a technique that can be utilized within the laboratory for gene regulation — however, it is not without limitations. Naturally occurring antisense RNAs have been isolated in a various microbes, including the *E. coli* RI plasmid, which uses a hok/sok system. A hok/sok system is a mechanism employed by *E. coli* that is used as a postsegregational killing mechanism. The hok gene is a toxic gene and the sok gene is an antitoxin. Hence, *E. coli* utilizing this system can regulate the expression of hok (toxin) and inhibits its translation by producing sok RNA (antitoxin). The outcome is the repression of hok mRNA translation.

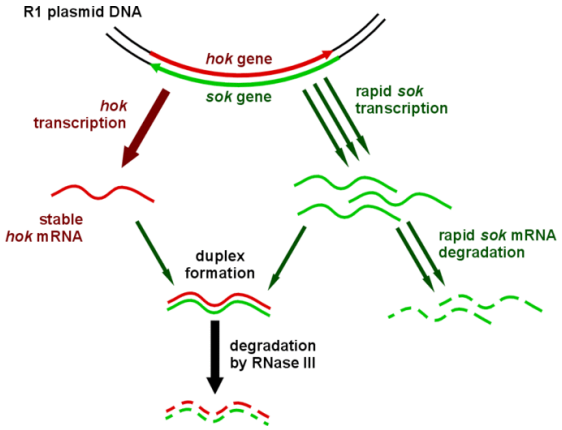

Figure: **Hok/sok System**: An example of a system found in nature that utilizes an antisense RNA to control gene regulation. The hok gene is a toxic gene that can be translationally repressed by the production of an antisense mRNA, sok (anti toxic).

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7.19B: Attenuation

Learning Objectives

- Compare transcriptional and translational attenuation

Attenuation is a regulatory mechanism used in bacterial operons to ensure proper transcription and translation. In bacteria, transcription and translation are capable of proceeding simultaneously. The need to prevent unregulated and unnecessary gene expression can be prevented by attenuation, which is characterized as a regulatory mechanism.

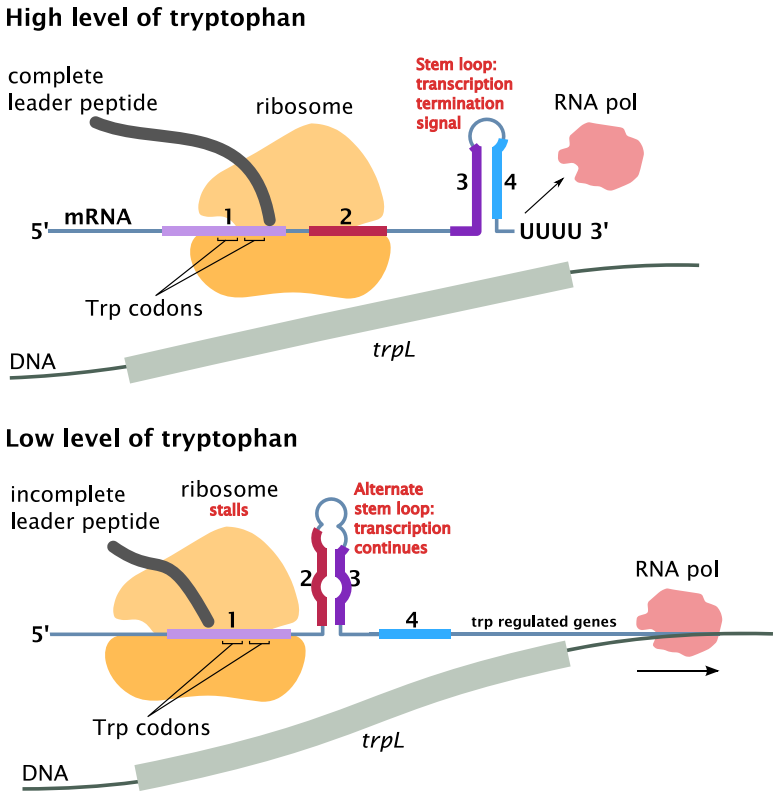

Figure: ***Attenuation of the Tryptophan Operon****: An example of attenuation is the tryptophan operon. This schematic represents transcriptional-attenuation as the formation of mRNA stem-loops prevents the continuance of transcription based on the levels of tryptophan in the metabolic environment.*

The process of attenuation involves the presence of a stop signal that indicates premature termination. The stop signal, referred to as the attenuator, prevents the proper function of the ribosomal complex, stopping the process. The attenuator is transcribed from the appropriate DNA sequence and its effects are dependent on the metabolic environment. In times of need, the attenuator within the mRNA sequence will be bypassed by the ribosome and proper translation will occur. However, if there is not a need for a mRNA molecule to be translated but the process was simultaneously initiated, the attenuator will prevent further transcription and cause a premature termination. Hence, attenuators can function in either transcription-attenuation or translation-attenuation.

Transcription-attenuation is characterized by the presence of 5′-cis acting regulatory regions that fold into alternative RNA structures which can terminate transcription. These RNA structures dictate whether transcription will proceed successfully or be terminated early, specifically, by causing transcription-attenuation. The result is a misfolded RNA structure where the Rho-independent terminator disrupts transcription and produced a non-functional RNA product. This characterizes the mechanisms of transcription-attenuation. The other RNA structure produced will be an anti-terminator that allows transcription to proceed.

Translation-attenuation is characterized by the sequestration of the *Shine-Dalgarno sequence*, which is a bacterial specific sequence that indicates the site for ribosomal binding to allow for proper translation to occur. However, in translation-attenuation, the attenuation mechanism results in the Shine-Dalgarno sequence forming as a hairpin-loop structure. The formation of this

hairpin-loop structure results in the inability of the ribosomal complexes to form and proceed with proper translation. Hence, this specific process is referred to as translation-attenuation.

Key Points

- Attenuators are characterized by the presence of stop signals within the DNA sequence that can result in either transcriptional-attenuation or translational-attenuation.
- Transcriptional-attenuation is characterized by the presence of an attenuator within the DNA sequence that results in formation of mRNA-stem loops that prevent further transcription from occurring. The non-functional RNA produced prevents proper transcription.
- Translational-attenuation is characterized by the misfolding of the Shine-Dalgarno sequence. The Shine-Dalgarno sequence, responsible for ribosomal binding to allow proper translation, is inaccessible because it is folded into a hairpin-loop structure, thus, translation cannot occur.

Key Terms

- **operons**: A unit of genetic material that functions in a coordinated manner and is transcribed as one unit.

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7.19C: Riboswitches

Learning Objectives

- Describe riboswitches

Riboswitches are specific components of an mRNA molecule that regulates gene expression. The riboswitch is a part of an mRNA molecule that can bind and target small target molecules. An mRNA molecule may contain a riboswitch that directly regulates its own expression. The riboswitch displays the ability to regulate RNA by responding to concentrations of its target molecule. The riboswitches are naturally occurring RNA molecules that allow for RNA regulation. Hence, the existence of RNA molecules provide evidence to the RNA world hypothesis that RNA molecules were the original molecules, and that proteins developed later in evolution.

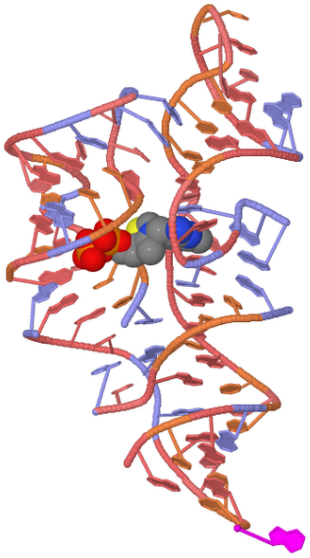

Figure: ***Example of a Riboswitch**: A 3D image of the riboswitch responsible for binding to thiamine pyrophosphate (TPP)*

Riboswitches are found in bacteria, plants, and certain types of fungi. The various mechanisms by which riboswitches function can be divided into two major parts including an aptamer and an expression platform. The aptamer is characterized by the ability of the riboswitch to directly bind to its target molecule. The binding of the aptamer to the target molecule results in a conformational change of the expression platform, thus affecting gene expression. The expression platforms, which control gene expression, can either be turned off or activated depending on the specific function of the small molecule. Various mechanisms by which riboswitches function include, but are not limited to the following:

- The ability to function as a ribozyme and cleave itself if a sufficient concentration of its metabolite is present
- The ability to fold the mRNA in such a way the ribosomal binding site is inaccessible and prevents translation from occurring
- The ability to affect the splicing of the pre-mRNA molecule

The riboswitch, dependent on its specific function, can either inhibit or activate gene expression.

Key Points

- The mechanisms by which riboswitches regulate RNA expression, can be divided into two major processes, including aptamer and expression platform.
- The aptamer is characterized by the direct binding of the small molecule to its target.
- The expression platform is characterized by the conformational change, which occurs in the target upon binding of an aptamer, resulting in either inhibition or activation of gene expression.

Key Terms

- **aptamer**: Any nucleic acid or protein that is used to bind to a specific target molecule.

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7.19D: Regulation of Sigma Factor Activity

Learning Objectives

- Analyze the regulation of sigma factor activation

Sigma factors are proteins that function in transcription initiation. Specifically, in bacteria, sigma factors are necessary for recognition of RNA polymerase to the gene promoter site. The sigma factor allows the RNA polymerase to properly bind to the promoter site and initiate transcription which will result in the production of an mRNA molecule. The type of sigma factor that is used in this process varies and depends on the gene and on the cellular environment. The sigma factors identified to date are characterized based on molecular weight and have shown diversity between bacterial species as well. Once the role of the sigma factor is completed, the protein leaves the complex and RNA polymerase will continue with transcription.

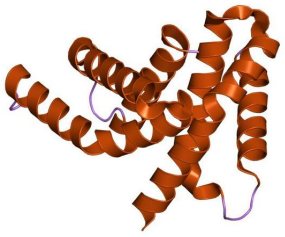

Figure: **Sigma factor SigR**: Structure of sigma factor.

The regulation of sigma factor activity is critical and necessary to ensure proper initiation of transcription. The activity of sigma factors within a cell is controlled in numerous ways. Sigma factor synthesis is controlled at the levels of both transcription and translation. Often times, sigma factor expression or activity is dependent on specific growth phase transitions of the organism. If transcription of genes involved in growth is necessary, the sigma factors will be translated to allow for transcription initiation to occur. However, if transcription of genes is not required, sigma factors will not be active.

In specific instances when transcriptional activity needs to be inhibited, there are anti-sigma factors which perform this function. The anti-sigma factors will bind to the RNA polymerase and prevent its binding to sigma factors present at the promoter site. The anti-sigma factors are responsible for regulating inhibition of transcriptional activity in organisms that require sigma factor for proper transcription initiation.

Key Points

- Sigma factor proteins promote binding of RNA polymerase to promoter sites within DNA sequences to allow for initiation of transcription.
- Sigma factors are specific for the gene and are affected by the cellular environment.
- Sigma factors can regulate at both a transcription and translational level.
- Anti-sigma factors are responsible for inhibiting sigma factor function thus, inhibiting transcription.

Key Terms

- **growth phase transitions**: The various phases required for bacterial growth include: lag, exponential, and stationary phases.

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7.19E: Regulation of Sigma Factor Translation

Sigma factors are proteins that regulate gene expression that are controlled at various levels, including at the translational level.

Learning Objectives

- Explain the regulation of sigma factor translation

Key Points

- Sigma factor expression is often associated with environmental changes that cause changes in gene expression.
- The translational control of sigma factors is critical in its role in transcription regulation.
- Sigma factor translation is controlled by small noncoding RNAs that can either activate or inhibit translation.

Key Terms

- **oxidative stress**: Damage caused to cells or tissue by reactive oxygen species.
- **sigma factor**: A sigma factor (σ factor) is a protein needed only for initiation of RNA synthesis.
- **RpoS protein**: RpoS is a central regulator of the general stress response and operates in both a retroactive and a proactive manner: not only does it allow the cell to survive environmental challenges, but it also prepares the cell for subsequent stresses (cross-protection).

Sigma factors are groups of proteins that regulate transcription and therefore function in house-keeping, metabolic, and regulation of growth processes in bacteria. Sigma factor expression is often associated with environmental changes that cause changes in gene expression. The regulation of expression of sigma factors occurs at transcriptional, translational, and post-translational levels as dictated by the cellular environment and the presence or absence of numerous cofactors.

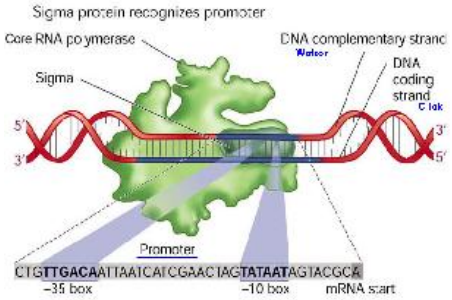

Figure: **Sigma Factor Regulation of Transcription**: An overview of how sigma factors regulate the transcriptional process.

Sigma factors include numerous types of factors. The most commonly studied sigma factors are often referred to as a RpoS proteins as the rpoS genes encode for sigma proteins of various sizes. In *E. coli*, the RpoS is the regulator of growth phase genes, specifically in the stationary phase. The RpoS is critical in the general stress responses and can either function in promoting survival during environmental stresses, but can also prepare the cell for stresses. Specifically, the translational control of the sigma factor is a major level of control.

The translational control of sigma factors involves the presence and function of small noncoding RNAs. Using RpoS proteins as the focus, the RpoS expression and transcription is regulated at the translational level. Small noncoding RNAs are able to sense environmental changes and stresses resulting in increased expression of RpoS protein. The small noncoding RNAs are able to specifically increase the amount of rpoS mRNA that undergoes translation.

The resultant increase of RpoS protein is based on the cellular environment and its needs. There are numerous classes of small noncoding RNAs that function in RpoS regulation, including DsrA, RprA and OxyS. These small noncoding RNAs are capable of sensing changes in temperature (DsrA), cell surface stress (RprA) and oxidative stress (OxyS). These RNAs can induce activation of rpoS translation. However, there are small noncoding RNAs, such as LeuO, that are capable of inhibiting rpoS translation as well via repression mechanisms. The regulation of rpoS translation is complex and involves cross-signaling and networking of numerous proteins and the regulatory small noncoding RNAs.

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7.19F: Proteolytic Degradation

Proteolytic degradation, or proteolysis, is a key factor that controls protein concentration and function.

LEARNING OBJECTIVES

Describe protein degradation

Key Takeaways

Key Points

- The major mechanism of proteolytic degradation utilized by the cell, is via the proteasomal pathway. Proteins that are degraded via the proteasomal complex are tagged via the addition of a ubiquitin signal.
- An additional mechanism utilized for proteolytic degradation is via the lysosomal pathway. The lysosome contains proteases which target proteins for degradation.
- Proteolysis is necessary to control protein concentration and prevent abnormal accumulation.
- Upon protein degradation, the amino acids are typically reused and recycled for the synthesis of new proteins.

Key Terms

- **ubiquitin**: A small regulatory protein sequence that directs proteins to specific compartments within the cell. Specifically, a ubiquitin tag directs the protein to a proteasome, which destroys and recycles the components.
- **proteases**: A class of enzymes that can cleave proteins.

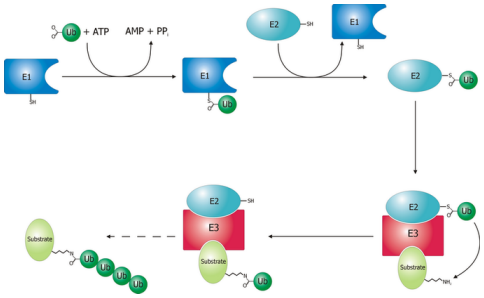

Figure: **The Process of Protein Degradation in a Proteosome**: Schematic of the proteolytic degradation pathway that utilizes proteasomal complexes. The protein is tagged with several ubiquitin signals that target the proteasome. Once the protein arrives at the proteasome, the protein is degraded into its amino acids which are then reused for synthesis of new proteins.

Proteolytic degradation is necessary in the regulation of cellular processes and function. The breakdown of proteins into smaller polypeptides, or its respective amino acids, are necessary for metabolic and cellular homeostasis. Polypeptides are commonly broken down via hydrolysis of the peptide bonds by utilizing a class of enzymes called *proteases*. However, proteolytic degradation can also occur utilizing various mechanisms, including intramolecular digestion and non-enzymatic methods. The mechanisms of proteolytic degradation are necessary for obtaining amino acids via degradation of digested proteins, preventing accumulation or abnormal concentrations of proteins, and by regulating cellular processes by removing proteins no longer needed.

Proteasomes are protein complexes that function in the degradation of unneeded or damaged proteins via proteolysis. The proteasomes are a major component of a complex and highly regulated mechanism. The proteasome is able to degrade proteins based on the presence of a *ubiquitin*protein. This ubiquitin sequence is a modification to proteins that are targeted for degradation. The recognition of this ubiquitin signal by the proteasome results in degradation of the protein into its amino acids, which are then recycled and reused for the synthesis of new proteins. The proteasomal degradation pathway is the major pathway utilized to ensure proteolytic degradation. It is necessary for homeostasis functioning in controlling cell cycle and gene expression, for example.

In addition to proteasomal complexes, the organelle, the lysosomes are also used to ensure protein degradation. The intracellular process that utilizes lysosomes involves autophagy. The lysosomal pathway, in comparison to the proteasomal pathway, is typically non-selective. The lysosome contains proteases that are able to target and degrade proteins.

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7.19G: Small Regulatory RNAs

Proteolytic degradation, or proteolysis, is a key factor that controls protein concentration and function.

LEARNING OBJECTIVES

Describe protein degradation

Key Takeaways

Key Points

- The major mechanism of proteolytic degradation utilized by the cell, is via the proteasomal pathway. Proteins that are degraded via the proteasomal complex are tagged via the addition of a ubiquitin signal.
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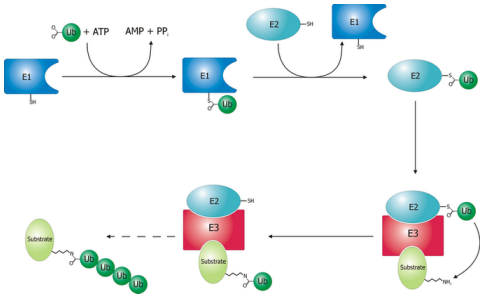

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SECTION OVERVIEW

7.20: Developmental Regulation

Topic hierarchy

7.20A: Sporulation in Bacillus

7.20B: Caulobacter Differentiation

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7.20A: Sporulation in Bacillus

Sporulation is the last-ditch response to starvation; it is suppressed until alternative responses prove inadequate.

Learning Objectives

- Explain sporulation in Bacillus

Key Points

- *B. subtilis* can divide symmetrically to make two daughter cells (binary fission), or asymmetrically, producing a single endospore that is resistant to environmental factors such as heat, desiccation, radiation, and chemical insult which can persist in the environment for long periods of time.
- The process of endospore formation has profound morphological and physiological consequences: radical post-replicative remodelling of two progeny cells, accompanied eventually by cessation of metabolic activity in one daughter cell (the spore) and death by lysis of the other (the ‘mother cell’).
- Sporulation in *B. subtilis* is induced by starvation; the sporulation developmental program is not initiated immediately when growth slows due to nutrient limitation.

Key Terms

- **endospore**: A dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.
- **sporulation**: The process of a bacterium becoming a spore.

Bacillus subtilis is a rod-shaped, Gram-postive bacteria that is naturally found in soil and vegetation. It is known for its ability to form a small, tough, protective, and metabolically dormant endospore. *B. subtilis* can divide symmetrically to make two daughter cells (binary fission), or asymmetrically, producing a single endospore that is resistant to environmental factors such as heat, desiccation, radiation, and chemical insult which can persist in the environment for long periods of time. The endospore is formed at times of nutritional stress, allowing the organism to persist in the environment until conditions become favourable. The process of endospore formation has profound morphological and physiological consequences: radical post-replicative remodeling of two progeny cells, accompanied eventually by cessation of metabolic activity in one daughter cell (the spore) and death by lysis of the other (the ‘mother cell’).

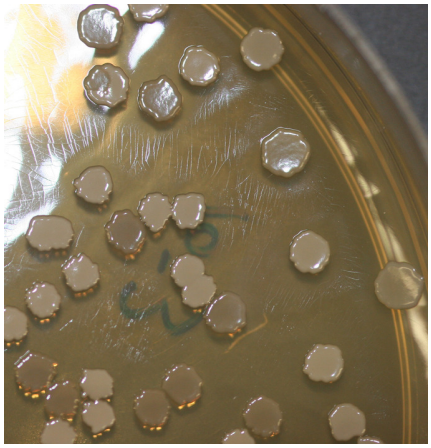

Figure: **B. subtillis**: Colonies of B. subtilis grown on a culture dish in a molecular biology laboratory.

Although sporulation in*B. subtilis* is induced by starvation, the sporulation developmental program is not initiated immediately when growth slows due to nutrient limitation. A variety of alternative responses can occur:

- The activation of flagellar motility to seek new food sources by chemotaxis
- The production of antibiotics to destroy competing soil microbes
- The secretion of hydrolytic enzymes to scavenge extracellular proteins and polysaccharides, or the induction of ‘competence’ for uptake of exogenous DNA for consumption, with the occasional side-effect that new genetic information is stably integrated.

Sporulation is a last-ditch response to starvation, and it is suppressed until alternative responses prove inadequate. Even then, certain conditions must be met, such as chromosome integrity, the state of chromosomal replication, and the functioning of the Krebs cycle.

Sporulation requires a great deal of time and energy, and it is essentially irreversible, making it crucial for a cell to monitor its surroundings efficiently and ensure that sporulation is embarked upon at only the most appropriate times. The wrong decision can be catastrophic: a vegetative cell will die if the conditions are too harsh, while bacteria-forming spores in an environment which is conducive to vegetative growth will be outcompeted. In short, initiation of sporulation is a very tightly regulated network with numerous checkpoints for efficient control.

Two transcriptional regulators, σH and Spo0A, play key roles in initiation of sporulation. Several additional proteins participate, mainly by controlling the accumulated concentration of Spo0A~P. Spo0A lies at the end of a series of inter-protein phosphotransfer reactions, Kin–Spo0F–Spo0B–Spo0A, termed as a ‘phosphorelay’.

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7.20B: Caulobacter Differentiation

A Caulobacter is used for studying the regulation of the cell cycle, asymmetric cell division, and cellular differentiation.

LEARNING OBJECTIVES

Explain how caulobacter serve as a model organism

Key Takeaways

Key Points

- The Caulobacter cell cycle regulatory system controls many modular subsystems that organize the progression of cell growth and reproduction.
- The central feature of the cell cycle regulation is a cyclical genetic circuit—a cell cycle engine –- that is centered around the successive interactions of four master regulatory proteins: DnaA, GcrA, CtrA, and CcrM.
- The interactions of four master regulatory proteins: DnaA, GcrA, CtrA, and CcrM directly control the timing of expression of over 200 genes. The four master regulatory proteins are synthesized and then eliminated from the cell one after the other over the course of the cell cycle.

Key Terms

- **senescence**: Ceasing to divide by mitosis because of shortening of telomeres or excessive DNA damage.
- **differentiation**: In cellular differentiation, a less specialized cell becomes a more specialized cell.
- **modular**: Consisting of separate modules; especially where each module performs or fulfills some specified function and could be replaced by a similar module for the same function, independently of the other modules.

Caulobacter crescentus is a Gram-negative, oligotrophic bacterium widely distributed in fresh water lakes and streams. Caulobacter is an important model organism for studying the regulation of the cell cycle, asymmetric cell division, and cellular differentiation. Caulobacter daughter cells have two very different forms. One daughter is a mobile “swarmer” cell that has a single flagellum at one cell pole that provides swimming motility for chemotaxis. The other daughter, called the “stalked” cell has a tubular stalk structure protruding from one pole that has an adhesive holdfast material on its end, with which the stalked cell can adhere to surfaces. Swarmer cells differentiate into stalked cells after a short period of motility. Chromosome replication and cell division only occurs in the stalked cell stage. Its name is due to the fact that it forms a crescent shape; crescentin is a protein that imparts this shape.

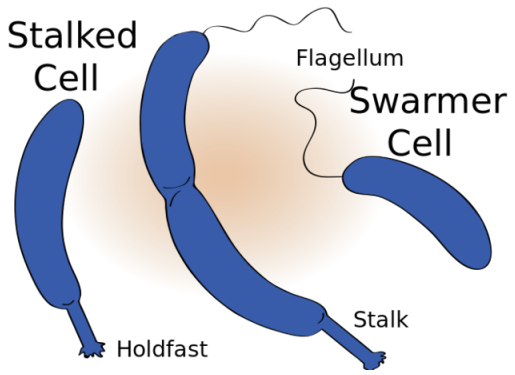

Figure: **Graphical representation of Caulobacter crescentus**: Swarmer cells differentiate into stalked cells after a short period of motility.

In the laboratory, researchers distinguish between *C. crescentus*strain CB15 (the strain originally isolated from a freshwater lake) and NA1000 (the primary experimental strain). In strain NA1000, which was derived from CB15 in the 1970’s, the stalked and predivisional cells can be physically separated in the laboratory from new swarmer cells, while cell types from strain CB15 cannot be physically separated. The isolated swarmer cells can then be grown as a synchronized cell culture. Detailed study of the molecular development of these cells as they progress through the cell cycle has enabled researchers to understand Caulobacter cell cycle regulation in great detail. Due to this capacity to be physically synchronized, strain NA1000 has become the predominant experimental Caulobacter strain throughout the world. Additional phenotypic differences between the two strains have subsequently accumulated due to selective pressures on the NA1000 strain in the laboratory environment. The genetic basis of the

phenotypic differences between the two strains results from coding, regulatory, and insertion/deletion polymorphisms at five chromosomal loci. "*C. Crescentus*" is synonymous with "Caulobacter Vibrioides. "

The Caulobacter cell cycle regulatory system controls many modular subsystems that organize the progression of cell growth and reproduction. A control system constructed using biochemical and genetic logic circuitry organizes the timing of initiation of each of these subsystems. The central feature of the cell cycle regulation is a cyclical genetic circuit—a cell cycle engine –- that is centered around the successive interactions of four master regulatory proteins: DnaA, GcrA, CtrA, and CcrM. These four proteins directly control the timing of expression of over 200 genes. The four master regulatory proteins are synthesized and then eliminated from the cell one after the other over the course of the cell cycle. Several additional cell signaling pathways are also essential to the proper functioning of this cell cycle engine.

The principal role of these signaling pathways is to ensure reliable production and elimination of the CtrA protein from the cell at just the right times in the cell cycle. An essential feature of the Caulobacter cell cycle is that the chromosome is replicated once and only once per cell cycle. This is in contrast to the E. coli cell cycle where there can be overlapping rounds of chromosome replication simultaneously underway. The opposing roles of the Caulobacter DnaA and CtrA proteins are essential to the tight control of Caulobacter chromosome replication. The DnaA protein acts at the origin of replication to initiate the replication of the chromosome. The CtrA protein, in contrast, acts to block initiation of replication, so it must be removed from the cell before chromosome replication can begin. Multiple additional regulatory pathways integral to cell cycle regulation and involving both phospho signaling pathways and regulated control of protein proteolysis act to assure that DnaA and CtrA are present in the cell exactly when they are needed.

Caulobacter was the first asymmetric bacterium shown to age. Reproductive senescence was measured as the decline in the number of progeny produced over time. A similar phenomenon has since been described in the bacterium Escherichia coli, which gives rise to morphologically similar daughter cells.

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SECTION OVERVIEW

7.21: Sensing and Signal Transduction

Topic hierarchy

7.21A: Chemotaxis

7.21B: Two-Component Regulatory Systems

7.21C: Quorum Sensing

7.21D: Control of Transcription in Archaea

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7.21A: Chemotaxis

Chemotaxis is the phenomenon whereby bacterial cells direct their movements according to certain chemicals in their environment.

LEARNING OBJECTIVES

Explain how chemotaxis works in bacteria that have flagella

Key Takeaways

Key Points

- Chemoattractants and chemorepellents are inorganic or organic substances possessing chemotaxis -inducer effect in motile cells.
- Some bacteria, such as E. coli, have several flagella that can rotate to facilitate chemotaxis.
- The overall movement of a bacterium is the result of alternating tumble and swim phases.

Key Terms

- **chemotaxis**: Chemotaxis is the phenomenon whereby somatic cells, bacteria, and other single-cell or multicellular organisms direct their movements in response to certain chemicals in their environment.
- **flagella**: A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells.
- **movement**: Physical motion between points in space.

Chemotaxis is the phenomenon whereby somatic cells, bacteria, and other single-cell or multicellular organisms direct their movements according to certain chemicals in their environment. This is important for bacteria to find food (for example, glucose) by swimming towards the highest concentration of food molecules, or to flee from poisons (for example, phenol).

Positive chemotaxis occurs if the movement is toward a higher concentration of the chemical in question. Conversely, negative chemotaxis occurs if the movement is in the opposite direction.

Chemoattractants and chemorepellents are inorganic or organic substances possessing chemotaxis-inducer effect in motile cells. Effects of chemoattractants are elicited via described or hypothetic chemotaxis receptors; the chemoattractant moiety of a ligand is target cell specific and concentration dependent. Most frequently investigated chemoattractants are formyl peptides and chemokines. Responses to chemorepellents result in axial swimming and they are considered a basic motile phenomena in bacteria. The most frequently investigated chemorepellents are inorganic salts, amino acids and some chemokines.

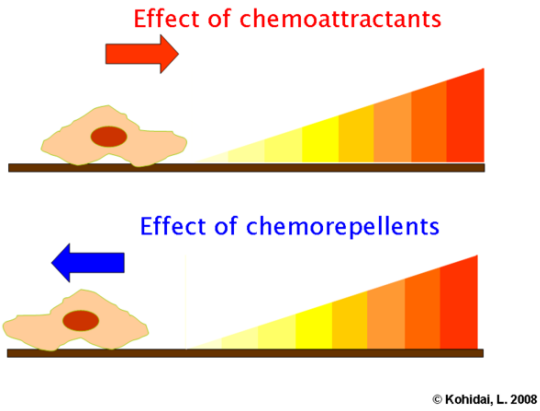

Figure: **Chemoattractants and chemorepellents**: In response to chemoattractants, cells move toward the stimulant. In response to chemorepellents, cells move away from them.

Some bacteria, such as E. coli, have several flagella per cell (4–10 typically). These can rotate in two ways:

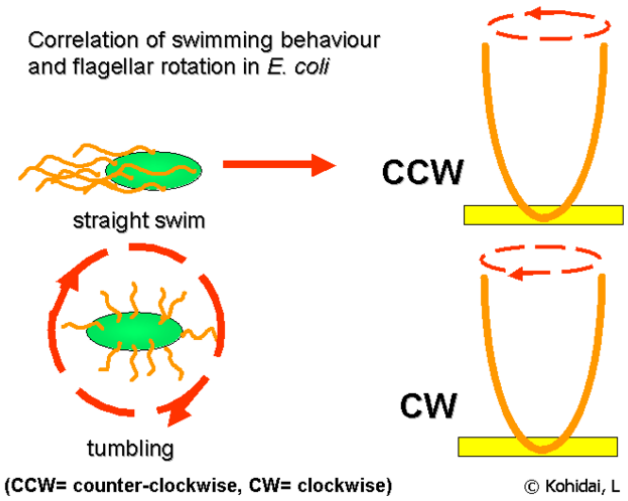

Figure: **Bacterial chemotaxis**: Correlation of swimming behavior and flagellar rotation in E. coli.

1. Counter-clockwise rotation – aligns the flagella into a single rotating bundle, causing the bacterium to swim in a straight line.

2. Clockwise rotation – breaks the flagella bundle apart such that each flagellum points in a different direction, causing the bacterium to tumble in place.

The directions of rotation are given for an observer outside the cell looking down the flagella toward the cell.

Overall movements in bacterium

This is the result of alternating tumble and swim phases. If one watches a bacterium swimming in a uniform environment, its movement will look like a random walk with relatively straight swims interrupted by random tumbles that reorient it. Bacteria such as *E. coli* are unable to choose the direction in which they swim, and are unable to swim in a straight line for more than a few seconds due to rotational diffusion: they "forget" the direction in which they are going. By repeatedly evaluating their course, and adjusting if they are moving in the wrong direction, bacteria can direct their motion to find favorable locations with high concentrations of attractants (usually food) and avoid repellents (usually poisons).

In the presence of a chemical gradient bacteria will chemotax, or direct their overall motion based on the gradient. If the bacterium senses that it is moving in the correct direction (toward attractant/away from repellent), it will keep swimming in a straight line for a longer time before tumbling. If it is moving in the wrong direction, it will tumble sooner and try a new direction at random. In other words, bacteria like *E. coli* use temporal sensing to decide whether their situation is improving or not. In this way, it finds the location with the highest concentration of attractant (usually the source) quite well. Even under very high concentrations, it can still distinguish very small differences in concentration. Fleeing from a repellent works with the same efficiency.

Purposeful random walk

This is a result of simply choosing between two methods of random movement; namely tumbling and straight swimming. In fact, chemotactic responses such as forgetting direction and choosing movements resemble the decision-making abilities of higher life-forms with brains that process sensory data.

The helical nature of the individual flagellar filament is critical for this movement to occur. As such, the protein that makes up the flagellar filament, flagellin, is quite similar among all flagellated bacteria. Vertebrates seem to have taken advantage of this fact by possessing an immune receptor (TLR5) designed to recognize this conserved protein.

As in many instances in biology, there are bacteria that do not follow this rule. Many bacteria, such as *Vibrio*, are monoflagellated and have a single flagellum at one pole of the cell. Their method of chemotaxis is different. Others possess a single flagellum that is kept inside the cell wall. These bacteria move by spinning the whole cell, which is shaped like a corkscrew.

Signal transduction in bacteria

The proteins CheW and CheA bind to the receptor. The activation of the receptor by an external stimulus causes autophosphorylation in the histidine kinase, CheA, at a single highly-conserved histidine residue. CheA in turn transfers phosphoryl groups to conserved aspartate residues in the response regulators CheB and CheY [*note*: CheA is a histidine kinase and

it does not actively transfer the phosphoryl group. The response regulator CheB takes the phosphoryl group from CheA]. This mechanism of signal transduction is called a two-component system and is a common form of signal transduction in bacteria.

CheY induces tumbling by interacting with the flagellar switch protein FliM, inducing a change from counter-clockwise to clockwise rotation of the flagellum. Change in the rotation state of a single flagellum can disrupt the entire flagella bundle and cause a tumble.

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7.21B: Two-Component Regulatory Systems

Two-component systems couple mechanism to allow organisms to sense and respond to changes in many different environmental conditions.

LEARNING OBJECTIVES

Describe the structure and function of a bacterial two-component regulatory system

Key Takeaways

Key Points

- Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions.
- Signal transduction can occur through the transfer of phosphoryl groups from adenosine triphosphate (ATP) to a specific histidine residue in the histidine kinases (HK).
- A variant of the two-component system is the phospho-relay system.

Key Terms

- **Two-component systems**: Two-component systems serve as a basic stimulus-response coupling mechanism to allow organisms to sense and respond to changes in many different environmental conditions. They typically consist of a membrane-bound histidine kinase that senses a specific environmental stimulus and a corresponding response regulator that mediates the cellular response, mostly through differential expression of target genes.
- **Signal transduction**: Signal transduction occurs when an extracellular signaling molecule activates a cell surface receptor. In turn, this receptor alters intracellular molecules creating a response.
- **histidine kinase**: Histidine Kinases (HK) are multifunctional, typically transmembrane, proteins of the transferase class that play a role in signal transduction across the cellular membrane.

Two-Component Systems

In molecular biology, two-component systems serve as a basic stimulus-response coupling mechanism allowing organisms to sense and respond to changes in many different environmental conditions. They typically consist of a membrane -bound histidine kinase that senses a specific environmental stimulus and a corresponding response regulator that mediates the cellular response. Two component signaling systems are widely occurring in prokaryotes whereas only a few two-component systems have been identified in eukaryotic organisms.

Signal transduction occurs through the transfer of phosphoryl groups from adenosine triphosphate (ATP) to a specific histidine residue in the histidine kinases (HK). This is an autophosphorylation reaction. Subsequently the histidine kinase catalyzes the transfer of the phosphate group on the phosphorylated histidine residues to an aspartic acid residue on the response regulator (RR). Phosphorylation causes the response regulator's conformation to change, usually activating an attached output domain, which then leads to the stimulation (or repression) of expression of target genes. The level of phosphorylation of the response regulator controls its activity. Some HK are bifunctional, catalysing both the phosphorylation and dephosphorylation of their cognate RR. The input stimuli can regulate either the kinase or phosphatase activity of the bifunctional HK.

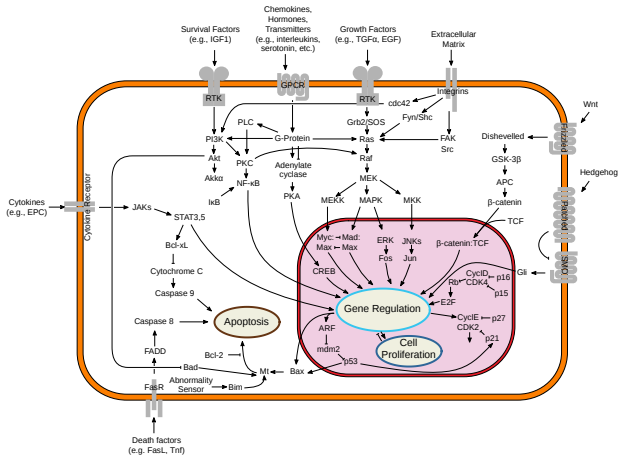

Figure: **Signal transduction**: An overview of major signal transduction pathways.

Two-component signal transduction systems enable bacteria to sense, respond and adapt to a wide range of environments, stressors and growth conditions. Some bacteria can contain as many as 200 two-component systems that need tight regulation to prevent unwanted cross-talk. These pathways have been adapted to respond to a wide variety of stimuli, including nutrients, cellular redox state, changes in osmolarity, quorum signals, antibiotics, temperature, chemoattractants, pH and more. In E. coli the EnvZ/OmpR osmoregulation system controls the differential expression of the outer membrane porin proteins OmpF and OmpC. The KdpD sensor kinase proteins regulate the kdpFABC operon responsible for potassium transport in bacteria including E. coli and Clostridium acetobutylicum. The N-terminal domain of this protein forms part of the cytoplasmic region of the protein, which may be the sensor domain responsible for sensing turgor pressure.

System Variants

A variant of the two-component system is the phospho-relay system. Here a hybrid HK autophosphorylates and then transfers the phosphoryl group to an internal receiver domain, rather than to a separate RR protein. The phosphoryl group is then shuttled to histidine phosphotransferase (HPT) and subsequently to a terminal RR, which can evoke the desired response.

Signal transducing histidine kinases are the key elements in two-component signal transduction systems. Examples of histidine kinases are EnvZ, which plays a central role in osmoregulation, and CheA, which plays a central role in the chemotaxis system. Histidine kinases usually have an N-terminal ligand-binding domain and a C-terminal kinase domain, but other domains may also be present. The kinase domain is responsible for the autophosphorylation of the histidine with ATP, the phosphotransfer from the kinase to an aspartate of the response regulator, and (with bifunctional enzymes) the phosphotransfer from aspartyl phosphate back to ADP or to water. The kinase core has a unique fold, distinct from that of the Ser/Thr/Tyr kinase superfamily.

HKs can be roughly divided into two classes: orthodox and hybrid kinases. Most orthodox HKs, typified by the Escherichia coli EnvZ protein, function as periplasmic membrane receptors and have a signal peptide and transmembrane segment(s) that separate the protein into a periplasmic N-terminal sensing domain and a highly conserved cytoplasmic C-terminal kinase core. Members of this family, however, have an integral membrane sensor domain. Not all orthodox kinases are membrane bound, e.g., the nitrogen regulatory kinase NtrB (GlnL) is a soluble cytoplasmic HK. Hybrid kinases contain multiple phosphodonor and phosphoacceptor sites and use multi-step phospho-relay schemes instead of promoting a single phosphoryl transfer. In addition to the sensor domain and kinase core, they contain a CheY-like receiver domain and a His-containing phosphotransfer (HPt) domain.

The Hpr Serine/threonine kinase PtsK is the sensor in a multicomponent phosphorelay system in control of carbon catabolic repression in bacteria. This kinase is unusual in that it recognizes the tertiary structure of its target and is a member of a novel family unrelated to any previously described protein phosphorylating enzymes. X-ray analysis of the full-length crystalline enzyme from Staphylococcus xylosus at a resolution of 1.95 A shows the enzyme to consist of two clearly separated domains that are assembled in a hexameric structure resembling a three-bladed propeller. The blades are formed by two N-terminal domains each, and the compact central hub assembles the C-terminal kinase domains.

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7.21C: Quorum Sensing

Quorum sensing is a system of stimulus and response correlated to population density.

LEARNING OBJECTIVES

Explain the mechanism of quorum sensing in bacteria

Key Takeaways

Key Points

- Some of the best-known examples of quorum sensing come from studies of bacteria.
- Bacteria use quorum sensing to coordinate certain behaviors based on the local density of the bacterial population.
- Bacteria that use quorum sensing constitutively produce and secrete certain signaling molecules (called autoinducers or pheromones).

Key Terms

- **quorum sensing**: Quorum sensing is a system of stimulus and response correlated to population density. Many species of bacteria use quorum sensing to coordinate gene expression according to the density of their local population.
- **density**: A measure of the amount of matter contained by a given volume.
- **population**: A collection of organisms of a particular species, sharing a particular characteristic of interest, most often that of living in a given area.

Quorum sensing is a system of stimulus and response correlated to population density. Many species of bacteria use quorum sensing to coordinate gene expression according to the density of their local population. In similar fashion, some social insects use quorum sensing to determine where to nest. In addition to its function in biological systems, quorum sensing has several useful applications for computing and robotics.

Quorum sensing can function as a decision-making process in any decentralized system, as long as individual components have: (a) a means of assessing the number of other components they interact with and (b) a standard response once a threshold number of components is detected.

Quorum sensing may be achieved by degrading the signalling molecule. Using a KG medium, quorum quenching bacteria can be readily isolated from various environments including that which has previously been considered as unculturable. Recently, a well-studied quorum quenching bacterium has been isolated and its AHL degradation kinetic has been studied by using rapid resolution liquid chromatography (RRLC).

Some of the best-known examples of quorum sensing come from studies of bacteria. Bacteria use quorum sensing to coordinate certain behaviors based on the local density of the bacterial population. Quorum sensing can occur within a single bacterial species as well as between diverse species, and can regulate a host of different processes, in essence, serving as a simple communication network. A variety of different molecules can be used as signals. Common classes of signaling molecules are oligopeptides in Gram-positive bacteria, N-Acyl Homoserine Lactones (AHL) in Gram-negative bacteria, and a family of autoinducers known as autoinducer-2 (AI-2) in both Gram-negative and Gram-positive bacteria.

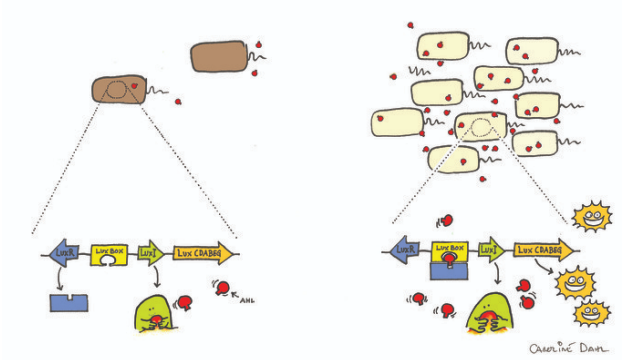

Figure: **Quorum Sensing**: Model of Quorum sensing.

Bacteria that use quorum sensing constitutively produce and secrete certain signaling molecules (called autoinducers or pheromones). These bacteria also have a receptor that can specifically detect the signaling molecule (inducer). When the inducer binds the receptor, it activates transcription of certain genes, including those for inducer synthesis. There is a low likelihood of a bacterium detecting its own secreted inducer. Thus, in order for gene transcription to be activated, the cell must encounter signaling molecules secreted by other cells in its environment. When only a few other bacteria of the same kind are in the vicinity, diffusion reduces the concentration of the inducer in the surrounding medium to almost zero, so the bacteria produce little inducer. However, as the population grows, the concentration of the inducer passes a threshold, causing more inducer to be synthesized. This forms a positive feedback loop, and the receptor becomes fully activated. Activation of the receptor induces the up-regulation of other specific genes, causing all of the cells to begin transcription at approximately the same time. This coordinated behavior of bacterial cells can be useful in a variety of situations. For instance, the bioluminescent luciferase produced by *Vibriofischeri* would not be visible if it were produced by a single cell. By using quorum sensing to limit the production of luciferase to situations when cell populations are large, V. fischeri cells are able to avoid wasting energy on the production of useless product.

Three-dimensional structures of proteins involved in quorum sensing were first published in 2001, when the crystal structures of three LuxS orthologs were determined by X-ray crystallography. In 2002, the crystal structure of the receptor LuxP of Vibrio harveyi with its inducer AI-2 (which is one of the few biomolecules containing boron) bound to it was also determined. Many bacterial species, including E. coli, an enteric bacterium and model organism for Gram-negative bacteria, produce AI-2. A comparative genomic and phylogenetic analysis of 138 genomes of bacteria, archaea, and eukaryotes found that “the LuxS enzyme required for AI-2 synthesis is widespread in bacteria, while the periplasmic binding protein LuxP is present only in Vibrio strains,” leading to the conclusion that either “other organisms may use components different from the AI-2 signal transduction system of Vibrio strains to sense the signal of AI-2 or they do not have such a quorum sensing system at all. ” Certain bacteria can produce enzymes called lactonases that can target and inactivate AHLs.

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7.21D: Control of Transcription in Archaea

Transcription and translation in archaea resemble these processes in eukaryotes more than in bacteria.

LEARNING OBJECTIVES

Compare the archaea with bacteria and eukaryotes in terms of their general mechanisms of gene expression

Key Takeaways

Key Points

- The proteins that archaea, bacteria and eukaryotes share form a common core of cell function, relating mostly to transcription, translation, and nucleotide metabolism.
- The archaean RNA polymerase and ribosomes are very close to their equivalents in eukaryotes.
- However, other archaean transcription factors are closer to those found in bacteria.

Key Terms

- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei that are fundamentally different from bacteria.
- **transcription**: Transcription is the process of creating a complementary RNA copy of a sequence of DNA. Both RNA and DNA are nucleic acids, which use base pairs of nucleotides as a complementary language that can be converted back and forth from DNA to RNA by the action of the correct enzymes.
- **eukaryotes**: A eukaryote is an organism whose cells contain complex structures enclosed within membranes. Eukaryotes may more formally be referred to as the taxon Eukarya or Eukaryota. The defining membrane-bound structure that sets eukaryotic cells apart from prokaryotic cells is the nucleus, or nuclear envelope, within which the genetic material is carried.

The Archaea constitute a domain of single-celled microorganisms. These microbes have no cell nucleus or any other membrane-bound organelles within their cells.

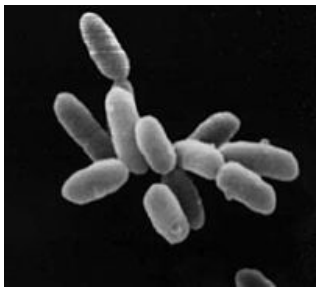

Figure: **Archaea**: An image of Halobacteria sp. strain NRC-1, each cell about 5 μm long

Archaea are genetically distinct from bacteria and eukaryotes, with up to 15% of the proteins encoded by any one archaeal genome being unique to the domain, even though most of these unique genes have no known function. Of the remainder of the unique proteins that have an identified function, most belong to the Euryarchaea and are involved in methanogenesis. The proteins that archaea, bacteria and eukaryotes share form a common core of cell function, relating mostly to transcription, translation, and nucleotide metabolism. Other characteristic archaean features are the organization of genes of related function—such as enzymes that catalyze steps in the same metabolic pathway into novel operons, and large differences in tRNA genes and their aminoacyl tRNA synthetases.

Transcription and translation in archaea resemble these processes in eukaryotes more than in bacteria, with the archaean RNA polymerase and ribosomes being very close to their equivalents in eukaryotes. Although archaea only have one type of RNA polymerase, its structure and function in transcription seems to be close to that of the eukaryotic RNA polymerase II, with similar protein assemblies (the general transcription factors) directing the binding of the RNA polymerase to a gene's promoter. However, other archaean transcription factors are closer to those found in bacteria. Post-transcriptional modification is simpler than in eukaryotes, since most archaean genes lack introns, although there are many introns in their transfer RNA and ribosomal RNA genes, and introns may occur in a few protein-encoding genes.

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SECTION OVERVIEW

7.22: Genomics and Proteomics

Topic hierarchy

7.22A: Microarrays and the Transcriptome

7.22B: Proteomics

7.22C: Metabolomics

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7.22A: Microarrays and the Transcriptome

Learning Objectives

- Define the transcriptome

The transcriptome is the set of all RNA molecules, including mRNA, rRNA, tRNA, and other non-coding RNA produced in one or a population of cells. The term can be applied to the total set of transcripts in a given organism, or to the specific subset of transcripts present in a particular cell type. Unlike the genome, which is roughly fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions. Because it includes all mRNA transcripts in the cell, the transcriptome reflects the genes that are being actively expressed at any given time, with the exception of mRNA degradation phenomena such as transcriptional attenuation.

Analysis of the Transcriptome

The study of transcriptomics, also referred to as expression profiling, examines the expression level of mRNAs in a given cell population, often using high-throughput techniques based on DNA microarray technology. A number of organism-specific transcriptome databases have been constructed and annotated to aid in the identification of genes that are differentially expressed in distinct cell populations.

DNA microarrays can provide a genome-wide method for comparison of the abundance of DNAs in the same samples.The DNA in spots can only be PCR products specific for individual genes. A DNA copy of RNA is made using the enzyme reverse transcriptase. Sequencing is now being used instead of gene arrays to quantify DNA levels, at least semi-quantitatively.

The transcriptomes of stem cells and cancer cells are of particular interest to researchers who seek to understand the processes of cellular differentiation and carcinogenesis. Analysis of the transcriptomes of human oocytes and embryos is used to understand the molecular mechanisms and signaling pathways controlling early embryonic development, and could theoretically be a powerful tool in making proper embryo selection during *in vitro* fertilization.

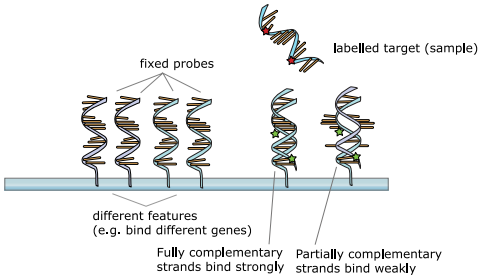

Figure: ***DNA microarray principle**: The core principle behind microarrays is hybridization between two DNA strands, the property of complementary nucleic acid sequences to specifically pair with each other by forming hydrogen bonds between complementary nucleotide base pairs.*

Key Points

- Unlike the genome, which is roughly fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions.
- The transcriptome reflects the genes that are being actively expressed at any given time.
- DNA microarrays can provide a method for comparing on a genome-wide basis the abundance of DNAs in a specific sample.

Key Terms

- **transcriptome**: The complete set of messenger RNA molecules (transcripts) produced in a cell or a population of cells.
- **DNA microarray**: a collection of microscopic DNA spots attached to a solid surface forming an array; used to measure the expression levels of large numbers of genes simultaneously
- **PCR**: polymerase chain reaction

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7.22B: Proteomics

Learning Objectives

- Summarize the purpose of, and methods used for, proteomics

Proteomics is the large-scale study of proteins, particularly their structures and functions. The proteome is the entire complement of proteins, including the modifications made to a particular set of proteins, produced by an organism or system. This will vary with time and distinct requirements, or stresses, that a cell or organism undergoes.

While proteomics generally refers to the large-scale experimental analysis of proteins, it is often specifically used for protein purification and mass spectrometry. After genomics and transcriptomics, proteomics is considered the next step in the study of biological systems. It is much more complicated than genomics mostly because while an organism's genome is more or less constant, the proteome differs from cell to cell and from time to time. This is because distinct genes are expressed in distinct cell types. This means that even the basic set of proteins which are produced in a cell needs to be determined. In the past, this was done by mRNA analysis, but this was found not to correlate with protein content. It is now known that mRNA is not always translated into protein. The amount of protein produced for a given amount of mRNA depends on the gene it is transcribed from and the current physiological state of the cell.

Proteomics confirms the presence of the protein and provides a direct measure of the quantity present. Not only does the translation from mRNA cause differences, but many proteins are also subjected to a wide variety of chemical modifications after translation which are critical to the protein's function such as phosphorylation, ubiquitination, methylation, acetylation, glycosylation, oxidation, and nitrosylation. Some proteins undergo ALL of these modifications, often in time-dependent combinations, aptly illustrating the potential complexity one has to deal with when studying protein structure and function.

Proteomics typically gives us a better understanding of an organism than genomics. First, the level of transcription of a gene gives only a rough estimate of its level of expression into a protein. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein. Second, as mentioned above many proteins experience post-translational modifications that profoundly affect their activities. For example, some proteins are not active until they become phosphorylated. Third, many transcripts give rise to more than one protein through alternative splicing or alternative post-translational modifications. Fourth, many proteins form complexes with other proteins or RNA molecules. They only function in the presence of these other molecules. Finally, protein degradation rate plays an important role in protein content.

One way in which a particular protein can be studied is to develop an antibody which is specific to that modification. For example, there are antibodies that only recognize certain proteins when they are tyrosine-phosphorylated, known as phospho-specific antibodies. There are also antibodies specific to other modifications. These can be used to determine the set of proteins that have undergone the modification of interest. For more quantitative determinations of protein amounts, techniques such as ELISAs can be used.

Most proteins function in collaboration with other proteins. One goal of proteomics is to identify which proteins interact. This is especially useful in determining potential partners in cell signaling cascades. Several methods are available to probe protein–protein interactions. The traditional method is yeast two-hybrid analysis. New methods include protein microarrays, immunoaffinity, and chromatography followed by mass spectrometry, dual polarisation interferometry, Microscale Thermophoresis, and experimental methods such as phage display and computational methods.



Figure: ***Robotic preparation of MALDI mass spectrometry samples****: Matrix-assisted laser desorption/ionization (MALDI) is a soft ionization technique used in mass spectrometry. It allows for the analysis of biomolecules and large organic molecules which tend to be fragile and fragment when ionized by more conventional ionization methods.*

One of the most promising developments to come from the study of human genes and proteins has been the identification of potential new drugs for the treatment of disease. This relies on genome and proteome information to identify proteins associated with a disease, which computer software can then use as targets for new drugs. For example, if a certain protein is implicated in a disease, its 3-D structure provides the information to design drugs to interfere with the action of the protein. A molecule that fits the active site of an enzyme, but cannot be released by the enzyme, will inactivate the enzyme. Understanding the proteome, the structure and function of each protein and the complexities of protein–protein interactions will be critical for developing the most effective diagnostic techniques and disease treatments in the future. Moreover, an interesting use of proteomics is using specific protein biomarkers to diagnose disease. A number of techniques allow testing for proteins produced during a particular disease, which helps to diagnose the disease quickly.

Key Points

- The proteome is the entire complement of proteins, including the modifications made to a particular set of proteins, produced by an organism or system.
- The proteome varies with time and distinct requirements, or stresses, that a cell or organism undergoes.
- Proteomics typically gives us a better understanding of an organism than genomics.

Key Terms

- **proteomics**: The branch of molecular biology that studies the set of proteins expressed by the genome of an organism.
- **genomics**: The study of the complete genome of an organism.
- **mass spectrometry**: An analytical technique that measures the mass/charge ratio of the ions formed when a molecule or atom is ionized, vaporized, and introduced into a vacuum. Mass spectrometry may also involve breaking molecules into fragments – thus enabling its structure to be determined.

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7.22C: Metabolomics

Learning Objectives

- Review metabolomics

Metabolomics is the scientific study of chemical processes involving metabolites. The metabolome represents the collection of all metabolites, which are the end products of cellular processes, in a biological cell, tissue, organ, or organism. Thus, while mRNA gene expression data and proteomic analyses do not tell the whole story of what might be happening in a cell, metabolic profiling can give an instantaneous snapshot of the physiology of that cell. One of the challenges of systems biology and functional genomics is to integrate proteomic, transcriptomic, and metabolomic information to give a more complete picture of living organisms.

History and Development

The idea that biological fluids reflect the health of an individual has existed for a long time. The term “metabolic profile” was introduced by Horning, et al. in 1971, after they demonstrated that gas chromatography- mass spectrometry (GC-MS;) could be used to measure compounds present in human urine and tissue extracts. GC-MS is a method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a test sample. Concurrently, NMR spectroscopy, which was discovered in the 1940s, was also undergoing rapid advances. In 1974, Seeley et al. demonstrated the utility of using NMR to detect metabolites in unmodified biological samples. This first study on muscle tissue highlighted the value of NMR, in that it was determined that 90% of cellular ATP is complexed with magnesium. As sensitivity has improved with the evolution of higher magnetic field strengths and magic-angle spinning, NMR continues to be a leading analytical tool to investigate metabolism.



Figure: ***Gas Chromatography–mass spectrometry****: Gas chromatography–mass spectrometry (GC-MS) is a method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a test sample.*

In 2005, the first metabolomics web database for characterizing human metabolites, METLIN, was developed in the Siuzdak laboratory at The Scripps Research Institute. METLIN contained over 10,000 metabolites and tandem mass spectral data. On January 23, 2007, the Human Metabolome Project, led by Dr. David Wishart of the University of Alberta, Canada, completed the first draft of the human metabolome, consisting of a database of approximately 2500 metabolites, 1200 drugs and 3500 food components.

As late as mid-2010, metabolomics was still considered an “emerging field”. Further, it was noted that further progress in the field was in large part the result of addressing otherwise “irresolvable technical challenges” through technical evolution of mass spectrometry instrumentation. The word was coined in analogy with transcriptomics and proteomics. Like the transcriptome and the proteome, the metabolome is dynamic, changing from second to second. Although the metabolome can be defined readily enough, it is not currently possible to analyse the entire range of metabolites by a single analytical method.

Metabolites are the intermediates and products of metabolism. Within the context of metabolomics, a metabolite is usually defined as any molecule less than 1 kDa in size. However, there are exceptions to this, depending on the sample and detection method. Macromolecules such as lipoproteins and albumin are reliably detected in NMR-based metabolomics studies of blood plasma. In plant-based metabolomics, it is common to refer to “primary metabolites,” which are directly involved in growth, development and reproduction, and “secondary metabolites,” which are indirectly involved in growth, development and reproduction. In contrast, in human-based metabolomics it is more common to describe metabolites as being either endogenous (produced by the host

organism) or exogenous. The metabolome forms a large network of metabolic reactions, where outputs from one enzymatic chemical reaction are inputs to other chemical reactions. Such systems have been described as hypercycles.

Separation methods: Gas chromatography, especially when interfaced with mass spectrometry (GC-MS), is one of the most widely used and powerful methods. It offers very high chromatographic resolution, but requires chemical derivatization for many biomolecules: only volatile chemicals can be analysed without derivatization.

Detection methods: Mass spectrometry (MS) is used to identify and to quantify metabolites after separation. Surface-based mass analysis has seen a resurgence in the past decade, with new MS technologies focused on increasing sensitivity, minimizing background, and reducing sample preparation.

Statistical methods: The data generated in metabolomics usually consist of measurements performed on subjects under various conditions. These measurements may be digitized spectra, or a list of metabolite levels. In its simplest form this generates a matrix with rows corresponding to subjects and columns corresponding to metabolite levels.

Key applications

- *Toxicity assessment/toxicology*. Metabolic profiling, especially of urine or blood plasma samples, can be used to detect the physiological changes caused by toxic insult of a chemical or mixture of chemicals. This is of particular relevance to pharmaceutical companies wanting to test the toxicity of potential drug candidates.
- *Functional genomics*. Metabolomics can be an excellent tool for determining the phenotype caused by a genetic manipulation, such as gene deletion or insertion. Sometimes this can be a sufficient goal in itself—for instance, to detect any phenotypic changes in a genetically-modified plant intended for human or animal consumption. More exciting is the prospect of predicting the function of unknown genes by comparison with the metabolic perturbations caused by deletion/insertion of known genes.

Key Points

- The metabolome represents the collection of all metabolites in a biological cell, tissue, organ or organism, which are the end products of cellular processes.
- Metabolites are the intermediates and products of metabolism.
- The metabolome forms a large network of metabolic reactions, where outputs from one enzymatic chemical reaction are inputs to other chemical reactions.
- NMR and Mass Spectroscopy are the most widely used techniques to identify metabolites.

Key Terms

- **metabolomics**: The study of the range of metabolites present in a person's body at normal times, and when suffering from specific diseases; may be useful as a diagnostic tool
- **mass spectrometry**: An analytical technique that measures the mass/charge ratio of the ions formed when a molecule or atom is ionized, vaporized, and introduced into a vacuum. Mass spectrometry may also involve breaking molecules into fragments – thus enabling its structure to be determined.
- **metabolite**: Any substance produced by, or taking part in, a metabolic reaction.

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SECTION OVERVIEW

7.23: Genetic Engineering Products

Topic hierarchy

7.23A: Overview of Biotechnology

7.23B: Applications of Genetic Engineering

7.23C: Biochemical Products of Recombinant DNA Technology

7.23D: Mammalian Gene Expression in Bacteria

7.23E: Mammalian Proteins and Products

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7.23A: Overview of Biotechnology

Biotechnology is the use of biological techniques and engineered organisms to make products or plants and animals that have desired traits.

Learning Objectives

- Describe the historical development of biotechnology

Key Points

- For thousands of years, humankind has used biotechnology in agriculture, food production, and medicine.
- In the late 20th and early 21st century, biotechnology has expanded to include new and diverse sciences such as genomics, recombinant gene technologies, applied immunology, and development of pharmaceutical therapies and diganostic tests.
- Biotechnology has applications in four major industrial areas, including health care (medical), crop production and agriculture, non food (industrial) uses of crops and other products (e.g. biodegradable plastics, vegetable oil, biofuels), and environmental uses.

Key Terms

- **nanotechnology**: the science and technology of creating nanoparticles and of manufacturing machines which have sizes within the range of nanometres

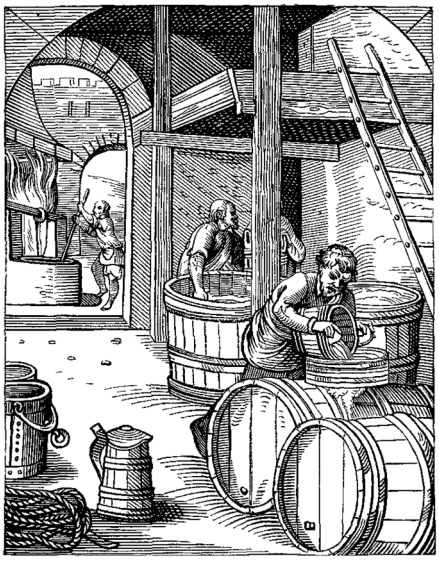

Figure: **Biotechnology**: Brewing (fermentation of beer) was an early application of biotechnology.

People have used biotechnology processes, such as selectively breeding animals and fermentation, for thousands of years. Late 19th and early 20^{th}century discoveries of how microorganisms carry out commercially useful processes and how they cause disease led to the commercial production of vaccines and antibiotics. Improved methods for animal breeding have also resulted from these efforts. Scientists in the San Francisco Bay Area took a giant step forward with the discovery and development of recombinant DNA techniques in the 1970s. The field of biotechnology continues to accelerate with new discoveries and new applications expected to benefit the economy throughout the 21st century.

In its broadest definition, biotechnology is the application of biological techniques and engineered organisms to make products or modify plants and animals to carry desired traits. This definition also extends to the use of various human cells and other body parts to produce desirable products. Bioindustry refers to the cluster of companies that produce engineered biological products and their supporting businesses. Biotechnology refers to the use of the biological sciences (such as gene manipulation), often in combination with other sciences (such as materials sciences, nanotechnology, and computer software), to discover, evaluate and develop products for bioindustry. Biotechnology products have made it easier to detect and diagnose illnesses. Many of these new techniques are easier to use and some, such as pregnancy testing, can even be used at home. More than 400 clinical diagnostic

devices using biotechnology products are in use today. The most important are screening techniques to protect the blood supply against contamination by AIDS and the hepatitis B and C viruses.

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7.23B: Applications of Genetic Engineering

Genetic engineering means the manipulation of organisms to make useful products and it has broad applications.

Learning Objectives

- Describe the major applications of genetic engineering

Key Points

- Genetic engineering has applications in medicine, research, industry and agriculture and can be used on a wide range of plants, animals and microorganisms.
- In medicine, genetic engineering has been used to mass-produce insulin, human growth hormones, follistim (for treating infertility), human albumin, monoclonal antibodies, antihemophilic factors, vaccines, and many other drugs.
- In research, organisms are genetically engineered to discover the functions of certain genes.
- Industrial applications include transforming microorganisms such as bacteria or yeast, or insect mammalian cells with a gene coding for a useful protein. Mass quantities of the protein can be produced by growing the transformed organism in bioreactors using fermentation, then purifying the protein.
- Genetic engineering is also used in agriculture to create genetically-modified crops or genetically-modified organisms.

Key Terms

- **biotechnology**: The use of living organisms (especially microorganisms) in industrial, agricultural, medical, and other technological applications.
- **cloning**: The production of a cloned embryo by transplanting the nucleus of a somatic cell into an ovum.

Genetic engineering, also called genetic modification, is the direct manipulation of an organism's genome using biotechnology.

New DNA may be inserted in the host genome by first isolating and copying the genetic material of interest, using molecular-cloning methods to generate a DNA sequence; or by synthesizing the DNA, and then inserting this construct into the host organism. Genes may be removed, or "knocked out", using a nuclease.



Figure: **Genetically manipulated mice**: Laboratory mice are genetically manipulated by deleting a gene for use in biomedical research.

Gene targeting is a different technique that uses homologous recombination to change an endogenous gene, and can be used to delete a gene, remove exons, add a gene, or introduce point mutations. Genetic engineering has applications in medicine, research, industry and agriculture and can be used on a wide range of plants, animals and microorganisms.

Genetic engineering has produced a variety of drugs and hormones for medical use. For example, one of its earliest uses in pharmaceuticals was gene splicing to manufacture large amounts of insulin, made using cells of E. coli bacteria. Interferon, which is used to eliminate certain viruses and kill cancer cells, also is a product of genetic engineering, as are tissue plasminogen activator and urokinase, which are used to dissolve blood clots.

Another byproduct is a type of human growth hormone; it's used to treat dwarfism and is produced through genetically-engineered bacteria and yeasts. The evolving field of gene therapy involves manipulating human genes to treat or cure genetic diseases and disorders. Modified plasmids or viruses often are the messengers to deliver genetic material to the body's cells, resulting in the production of substances that should correct the illness. Sometimes cells are genetically altered inside the body; other times scientists modify them in the laboratory and return them to the patient's body.

Since the 1990s, gene therapy has been used in clinical trials to treat diseases and conditions such as AIDS, cystic fibrosis, cancer, and high cholesterol. Drawbacks of gene therapy are that sometimes the person's immune system destroys the cells that have been genetically altered, and also that it is hard to get the genetic material into enough cells to have the desired effect.

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7.23C: Biochemical Products of Recombinant DNA Technology

Many practical applications of recombinant DNA are found in human and veterinary medicine, in agriculture, and in bioengineering.

Learning Objectives

- Describe the advances made possible by recombinant DNA technology

Key Points

- Recombinant DNA (rDNA) is widely used in biotechnology, medicine and research. Proteins and other products that result from the use of rDNA technology are found in essentially every western pharmacy, doctor's or veterinarian's office, medical testing laboratory, and biological research laboratory.
- Organisms that have been manipulated using recombinant DNA technology, and products derived from those organisms have found their way into many farms, supermarkets, home medicine cabinets, and even pet shops.
- Biochemical products of recombinant DNA technology in medicine and research include: human recombinant insulin, growth hormone, blood clotting factors, hepatitis B vaccine, and diagnosis of HIV infection.
- Biochemical products of recombinant DNA technology in agriculture include: golden rice, herbicide-resistant crops, and insect-resistant crops.

Key Terms

- **retinoblastoma**: A malignant tumour of the retina; a hereditary condition found mostly in children.
- **neurofibromatosis**: A genetic disorder characterized by the presence of multiple neurofibromas under the skin
- **cystic fibrosis**: An inherited condition in which the exocrine glands produce abnormally viscous mucus, causing chronic respiratory and digestive problems.
- **recombinant DNA technology**: the process of taking a gene from one organism and inserting it into the DNA of another

Recombinant DNA technology is the latest biochemical analysis that came about to satisfy the need for specific DNA segments. In this process, surrounding DNA from an existing cell is clipped in the desired amount of segments so that it can be copied millions of times.

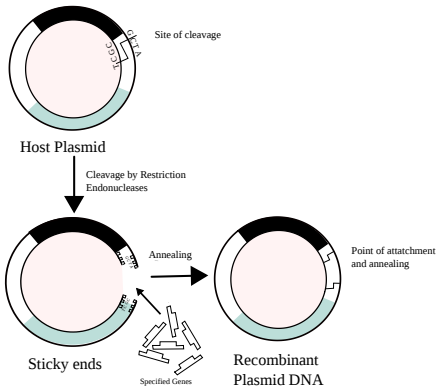

Figure: **Construction of recombinant DNA**: A foreign DNA fragment is inserted into a plasmid vector. In this example, the gene indicated by the white color is inactivated upon insertion of the foreign DNA fragment.

Recombinant DNA technology engineers microbial cells for producing foreign proteins, and its success solely depends on the precise reading of equivalent genes made with the help of bacterial cell machinery. This process has been responsible for fueling many advances related to modern molecular biology. The last two decades of cloned-DNA sequence studies have revealed detailed knowledge about gene structure as well as its organization. It has provided hints to regulatory pathways with the aid of which gene expression in myriad cell types is controlled by the cells, especially in those organisms having body plan with basic vertebrae structure.

Recombinant DNA technology, apart from being an important tool of scientific research, has also played a vital role in the diagnosis and treatment of various diseases, especially those belonging to genetic disorders.

Some of the recent advances made possible by recombinant DNA technology are:

1. Isolating proteins in large quantities: many recombinant products are now available, including follicle stimulating hormone (FSH), Follistim AQ vial, growth hormone, insulin and some other proteins.

2. Making possible mutation identification: due to this technology, people can be easily tested for mutated protein presence that can lead to breast cancer, neurofibromatosis, and retinoblastoma.

3. Hereditary diseases carrier diagnosis: tests now available to determine if a person is carrying the gene for cystic fibrosis, the Tay-Sachs diseases, Huntington's disease or Duchenne muscular dystrophy.

4. Gene transfer from one organism to other: the advanced gene therapy can benefit people with cystic fibrosis, vascular disease, rheumatoid arthritis and specific types of cancers.

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7.23D: Mammalian Gene Expression in Bacteria

Bacterial genetics can be manipulated to allow for mammalian gene expression systems established in bacteria.

Learning Objectives

- Describe the sequence of events in a genetically engineered expression system

Key Points

- Recently improved methods of DNA chemical synthesis, combined with recombinant DNA technology, permit the design and relatively rapid synthesis of modest-sized genes that can be incorporated into prokaryotic cells for gene expression using genetic engineering.
- The feasibility of this general approach was first demonstrated by the synthesis and expression of the mammalian peptide somatostatin in Escherichia coli.
- Mammalian gene expression can be achieved in many expression hosts by utilizing the host's naturally occurring machinery.

Key Terms

- **ribozyme**: A fragment of RNA that can act as an enzyme.
- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.

Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins and are produced after the process of translation. An expression system that is categorized as a genetic engineering product is a system specifically designed for the production of a gene product of choice. This is normally a protein, although may also be RNA, such as tRNA or a ribozyme.

The genetically engineered expression system contains the appropriate DNA sequence for the gene of choice which is engineered into a plasmid that is introduced into a bacteria host. The molecular machinery that is required to transcribe the DNA is derived from the innate and naturally occurring machinery in the host. The DNA is then transcribed into mRNA and then translated into protein products.

In a genetically engineered system, this entire process of gene expression may be induced depending on the plasmid used. In the broadest sense, mammalian gene expression includes every living cell but the term is more normally used to refer to expression as a laboratory tool. An expression system is therefore often artificial in some manner. Viruses and bacteria are an excellent example of expression systems.

The oldest and most widely used expression systems are cell-based. Expression is often done to a very high level and therefore referred to as overexpression. There are many ways to introduce foreign DNA to a cell for expression, and there are many different host cells which may be used for expression. Each expression system also has distinct advantages and liabilities.

Expression systems are normally referred to by the host and the DNA source or the delivery mechanism for the genetic material. For example, common bacterial hosts are E.coli and B. subtilis. With E. coli, DNA is normally introduced in a plasmid expression vector. The techniques for overexpression in E. coli work by increasing the number of copies of the gene or increasing the binding strength of the promoter region so as to assist transcription.

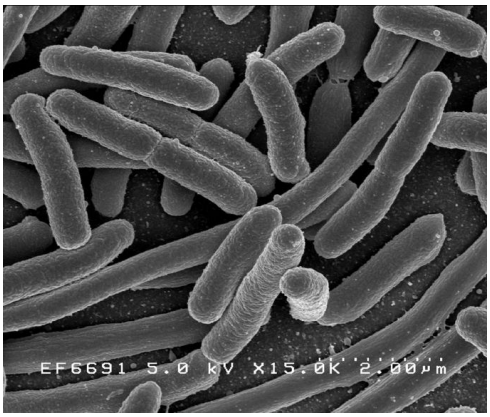

Figure: **Bacterial Flora**: E. coli is one of the most popular hosts for artificial gene expression.

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7.23E: Mammalian Proteins and Products

Genetic engineering enables scientists to create plants, animals, and microorganisms by manipulating genes.

Learning Objectives

- Explain the advantages and disadvantages of producing genetically engineered proteins in bacteria

Key Points

- Systems used for mass production of recombinant human proteins include bacteria, viruses, mammalian cells, animals, and plants.
- Most processes come with advantages and disadvantages, mostly low cost. However, mammalian proteins and products produced in animals bare ethical issues.
- A large number of mammalian proteins are being manufactured by pharmaceutical companies for use in the treatment of human diseases.

Key Terms

- **bioreactors**: A device that supports a biologically active environment.

The first successful products of genetic engineering were protein drugs like insulin, which is used to treat diabetes, and growth hormone somatotropin. These proteins are made in large quantities by genetically engineered bacteria or yeast in large “bioreactors. ” Some drugs are also made in transgenic plants, such as tobacco. Other human proteins that are used as drugs require biological modifications that only the cells of mammals, such as cows, goats, and sheep, can provide. For these drugs, production in transgenic animals is a good option. Using farm animals for drug production has many advantages because they are reproducible, have flexible production, are easily maintained, and have a great delivery method (e.g. milk).



Figure: **Synthetic Insulin**: human insulin produced by recombinant DNA technology.

Recombinant DNA technology not only allows therapeutic proteins to be produced on a large scale but using the same methodology protein molecules may be purposefully engineered. Genetic modifications introduced to a protein have many advantages over chemical modifications. Genetically engineered entities are biocompatible and biodegradable. The changes are introduced in 100% of the molecules with the exclusion of rare errors in gene transcription or translation. The preparations do not contain residual amounts of harsh chemicals used in the conjugation process. Bacterial expression systems, due to their simplicity, are often not able to produce a recombinant human protein identical to the naturally occurring wild type. Bacteria did not develop sophisticated mechanisms for performing post-translational modifications that are present in higher organisms. As a consequence, an increasing number of protein therapeutics is expressed in mammalian cells. However the low cost and simplicity of cultivating bacteria is an unbeatable advantage over any other expression system and therefore E. coli is always a preferable choice both on a lab scale and in industry.

Many mammalian proteins are produced by genetic engineering. These include, in particular, an assortment of hormones and proteins for blood clotting and other blood processes. For example, tissue plasminogen activator (TPA) is a blood protein that scavenges and dissolves blood clots that may form in the final stages of the healing process. TPA is primarily used in heart patients or others suffering from poor circulation to prevent the development of clots that can be life-threatening. Heart disease is a leading cause of death in many developed countries, especially in the United States, so microbially produced TPA is in high demand. In contrast to TPA, the blood clotting factors VII, VIII, and IX are critically important for the formation of blood clots. Hemophiliacs suffer from a deficiency of one or more clotting factors and can therefore be treated with microbially produced clotting factors. In the past hemophiliacs have been treated with clotting factor extracts from pooled human blood, some of which was contaminated

with viruses such as HIV and hepatitis C, putting hemophiliacs at high risk for contracting these diseases. Recombinant clotting factors have eliminated this problem.

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SECTION OVERVIEW

7.24: Transgenic Organisms

Topic hierarchy

7.24A: Genetically Engineered Vaccines

7.24B: Genetic Engineering in Animals

7.24C: Biotechnology in Medicine

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7.24A: Genetically Engineered Vaccines

Genetic engineering can be used to manufacture new vaccines.

Learning Objectives

- Evaluate genetically engineered vaccines

Key Points

- All vaccines are genetically modified in a way. A gene may be programmed to produce an antiviral protein in a bacterial cell. Once sealed into the DNA, the bacteria is now effectively re-programmed to replicate this new antiviral protein.
- Recombinant engineered vaccines are being extensively explored, especially to eradicate infectious diseases, allergies, and cancers.
- Protocols for genetically engineered vaccines raise issues on their efficacy and overall benefit.

Key Terms

- **FDA**: Food and Drug Administration, an agency of the United States Department of Health and Human Services.
- **vaccine**: a substance given to stimulate the body's production of antibodies and provide immunity against a disease, prepared from the agent that causes the disease, or a synthetic substitute.
- **genetic engineering**: The deliberate modification of the genetic structure of an organism. The term genetic modification is used as a synonym.

Genetic engineering, also called genetic modification, is the direct manipulation of an organism 's genome using biotechnology. New DNA may be inserted in the host genome by first isolating and copying the genetic material of interest using molecular cloning methods to generate a DNA sequence, or by synthesizing the DNA and then inserting this construct into the host organism. Genes may be removed, or "knocked out," using a nuclease. Gene targeting is a different technique that uses homologous recombination to change an endogenous gene, and can be used to delete a gene, remove exons, add a gene, or introduce point mutations.

Genetic engineering alters the genetic makeup of an organism using techniques that remove heritable material, or that introduce DNA prepared outside the organism either directly into the host or into a cell that is then fused or hybridized with the host. This involves using recombinant nucleic acid (DNA or RNA) techniques to form new combinations of heritable genetic material, followed by the incorporation of that material either indirectly through a vector system or directly through micro-injection, macro-injection and micro-encapsulation techniques.

In medicine, genetic engineering has been used to mass-produce insulin, human growth hormones, follistim (for treating infertility), human albumin, monoclonal antibodies, antihemophilic factors, vaccines,and many other drugs. Vaccination generally involves injecting weak live, killed, or inactivated forms of viruses or their toxins into the person being immunized. Genetically engineered viruses are being developed that can still confer immunity, but lack the infectious sequences. Mouse hybridomas, cells fused together to create monoclonal antibodies have been humanised through genetic engineering to create human monoclonal antibodies.



Figure: **Genetically modified viruses**: Scientist studying the H5N1 influenza virus to design a vaccine.

The process of genetic engineering involves splicing an area of a chromosome, a gene, that controls a certain characteristic of the body. The enzyme endonuclease is used to split a DNA sequence and to split the gene from the rest of the chromosome. For example, this gene may be programmed to produce an antiviral protein. This gene is removed and can be placed into another organism. For example, it can be placed into a bacteria, where it is sealed into the DNA chain using ligase. When the chromosome is once again sealed, the bacteria is now effectively re-programmed to replicate this new antiviral protein. The bacteria can continue to live a healthy life, though genetic engineering and human intervention has actively manipulated what the bacteria actually is.

Despite the early success demonstrated with the hepatitis B vaccine, no other recombinant engineered vaccine has been approved for use in humans. It is unlikely that a recombinant vaccine will be developed to replace an existing licensed human vaccine with a proven record of safety and efficacy. This is due to the economic reality of making vaccines for human use. Genetically engineered subunit vaccines are more costly to manufacture than conventional vaccines, since the antigen must be purified to a higher standard than was demanded of older, conventional vaccines. Each vaccine must also be subjected to extensive testing and review by the FDA, as it would be considered a new product. This is costly to a company in terms of both time and money and is unnecessary if a licensed product is already on the market. Although recombinant subunit vaccines hold great promise, they do present some potential limitations.

In addition to being less reactogenic, recombinant subunit vaccines have a tendency to be less immunogenic than their conventional counterparts. This can be attributed to these vaccines being held to a higher degree of purity than was traditionally done for an earlier generation of licensed subunit vaccines. Ironically, the contaminants often found in conventional subunit vaccines may have aided in the inflammatory process, which is essential for initiating a vigorous immune response. This potential problem may be overcome by employing one of the many new types of adjuvants that are becoming available for use in humans. Recombinant subunit vaccines may also suffer from being too well-defined, because they are composed of a single antigen. In contrast, conventional vaccines contain trace amounts of other antigens that may aid in conferring an immunity to infectious agents that is more solid than could be provided by a monovalent vaccine. This problem can be minimized, where necessary, by creating recombinant vaccines that are composed of multiple antigens from the same pathogen.

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7.24B: Genetic Engineering in Animals

The purpose of genetic engineering in animals is to create animals with special characteristics.

Learning Objectives

- Justify genetic engineering in animals

Key Points

- Genetic engineering of animals involves manipulating or modifying the genetic code of selected animals to alter their characteristics and to introduce certain desired traits.
- The genetic engineering in animals has increased significantly in recent years, and the use of this technology brings with it ethical issues, some of which relate to animal welfare.
- Biomedical applications of genetically engineered animals are numerous, and include understanding of gene function, modeling of human disease to either understand disease mechanisms or to aid drug development, and xenotransplantation.

Key Terms

- **ecosystem**: The interconnectedness of plants, animals, and microbes with each other and their environment.
- **Patents**: A form of intellectual property.

Scientists are now capable of creating new species of animals by taking genetic material from one, or more, plants or animals, and genetically engineering them into the genes of another animal. This allows scientists to create animals that are completely foreign to the earth and specifically tailored to possess only the traits that humans desire in animals. This means that science can engineer farm animals to grow faster, have healthier meat and flesh, and be less able to feel the pain and suffering often associated with the conditions present in modern factory farms.



Figure: **Genetically manipulated mice**: Laboratory mice are genetically manipulated by deleting a gene for use in biomedical research.

Genetically engineered animals are also created to help medical researchers in their quest to find cures for genetic disease, like breast cancer. Finally, endangered animal species can be cloned, thus helping wildlife management in its goals of preserving wild populations of the earth's biological diversity, and by ensuring that endangered animals' genetic information will not be lost when the last of the species dies.

This use of modern technology is not without its drawbacks or its critics. By genetically engineering farm and research animals, critics argue, we may be undoing what nature has worked to create over millions of years. Natural animals are specifically adapted to a given environment and when science manipulates the genes of a few species in the ecosystem, the entire balance of the ecosystem might fall completely apart and cause an unknown number of natural animal species to grow extinct.

Others argue that animals should possess, at a bare minimum, the right to be free of genetic manipulation or a reduction in their natural abilities. Despite this debate, the law in both the United States and in Europe, tends to support genetic engineering research and development by allowing genetically engineered animals to be patented. Patents give scientists a monopoly over their genetically engineered animal species, something before unheard of in modern economic systems. Typically, animals could be owned, but never entire species.

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7.24C: Biotechnology in Medicine

From manipulation of mutant genes to enhanced resistance to disease, biotechnology has allowed advances in medicine.

Learning Objectives

- Give examples of how biotechnology is used in medicine.

Key Points

- The study of pharmacogenomics can result in the development of tailor-made vaccines for people, more accurate means of determining drug dosages, improvements in drug discovery and approval, and the development of safer vaccines.
- Modern biotechnology can be used to manufacture drugs more easily and cheaply, as they can be produced in larger quantities from existing genetic sources.
- Genetic diagnosis involves the process of testing for suspected genetic defects before administering treatment through genetic testing.
- In gene therapy, a good gene is introduced at a random location in the genome to aid the cure of a disease that is caused by a mutated gene.

Key Terms

- **gene therapy**: any of several therapies involving the insertion of genes into a patient's cells in order to replace defective ones
- **pharmacogenomics**: the study of genes that code for enzymes that metabolize drugs, and the design of tailor-made drugs adapted to an individual's genetic make-up
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

Biotechnology in Medicine

It is easy to see how biotechnology can be used for medicinal purposes. Knowledge of the genetic makeup of our species, the genetic basis of heritable diseases, and the invention of technology to manipulate and fix mutant genes provides methods to treat the disease.

Pharmacogenomics is the study of how the genetic inheritance of an individual affects his/her body's response to drugs. It is a coined word derived from the words "pharmacology" and " genomics ". It is, therefore, the study of the relationship between pharmaceuticals and genetics. The vision of pharmacogenomics is to be able to design and produce drugs that are adapted to each person's genetic makeup. Pharmacogenomics results in the following benefits:

1. Development of tailor-made medicines. Using pharmacogenomics, pharmaceutical companies can create drugs based on the proteins, enzymes, and RNA molecules that are associated with specific genes and diseases. These tailor-made drugs promise not only to maximize therapeutic effects, but also to decrease damage to nearby healthy cells.

2. More accurate methods of determining appropriate drug dosages. Knowing a patient's genetics will enable doctors to determine how well the patient's body can process and metabolize a medicine. This will maximize the value of the medicine and decrease the likelihood of overdose.

3. Improvements in the drug discovery and approval process. The discovery of potential therapies will be made easier using genome targets. Genes have been associated with numerous diseases and disorders. With modern biotechnology, these genes can be used as targets for the development of effective new therapies, which could significantly shorten the drug discovery process.

4. Better vaccines. Safer vaccines can be designed and produced by organisms transformed by means of genetic engineering. These vaccines will elicit the immune response without the attendant risks of infection. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of pathogen at once.

Modern biotechnology can be used to manufacture existing drugs more easily and cheaply. The first genetically-engineered products were medicines designed to combat human diseases. In 1978, Genentech joined a gene for insulin with a plasmid vector and put the resulting gene into a bacterium called *Escherichia coli*. Insulin, widely used for the treatment of diabetes, was previously extracted from sheep and pigs. It was very expensive and often elicited unwanted allergic responses. The resulting genetically-engineered bacterium enabled the production of vast quantities of human insulin at low cost. Since then, modern biotechnology has made it possible to produce more easily and cheaply the human growth hormone, clotting factors for

hemophiliacs, fertility drugs, erythropoietin, and other drugs. Genomic knowledge of the genes involved in diseases, disease pathways, and drug-response sites are expected to lead to the discovery of thousands more new targets.

Genetic Diagnosis and Gene Therapy

The process of testing for suspected genetic defects before administering treatment is called genetic diagnosis by genetic testing. Depending on the inheritance patterns of a disease-causing gene, family members are advised to undergo genetic testing. Treatment plans are based on the findings of genetic tests that determine the type of cancer. If the cancer is caused by inherited gene mutations, other female relatives are also advised to undergo genetic testing and periodic screening for breast cancer. Genetic testing is also offered for fetuses to determine the presence or absence of disease-causing genes in families with specific, debilitating diseases.

Genetic testing involves the direct examination of the DNA molecule itself. A scientist scans a patient's DNA sample for mutated sequences. There are two major types of gene tests. In the first type, a researcher may design short pieces of DNA whose sequences are complementary to the mutated sequences. These probes will seek their complement among the base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and flag the mutation. In the second type, a researcher may conduct the gene test by comparing the sequence of DNA bases in a patient's gene to a normal version of the gene.

Gene therapy is a genetic engineering technique used to cure disease. In its simplest form, it involves the introduction of a good gene at a random location in the genome to aid the cure of a disease that is caused by a mutated gene. The good gene is usually introduced into diseased cells as part of a vector transmitted by a virus that can infect the host cell and deliver the foreign DNA. More advanced forms of gene therapy try to correct the mutation at the original site in the genome, such as is the case with treatment of severe combined immunodeficiency (SCID).

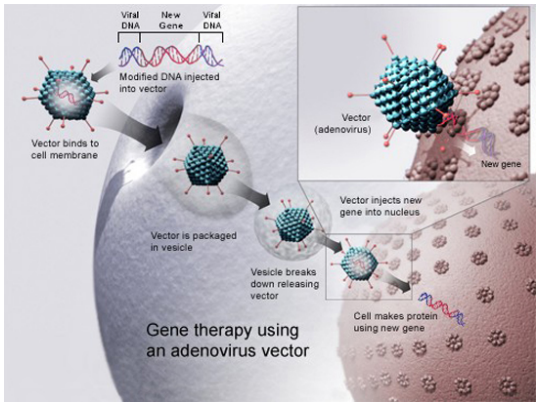

Figure: **Gene Therapy**: Gene therapy using an adenovirus vector can be used to cure certain genetic diseases in which a person has a defective gene.

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SECTION OVERVIEW

7.25: Molecular Techniques

Topic hierarchy

7.25A: Inactivating and Marking Target Genes with Transposons

7.25B: DNA Sequencing of Insertion Sites

7.25C: Northern Blots

7.25D: Western Bolts

7.25E: DNA Mobility Shifts

7.25F: Purifying Proteins by Affinity Tag

7.25G: Primer Extension Analysis

7.25H: DNA Protection Analysis

7.25I: Whole-Genome DNA-Binding Analysis

7.25J: Two-Hybrid Analysis

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7.25A: Inactivating and Marking Target Genes with Transposons

Transposons allow genes to be transferred to a host organism's chromosome, interrupting or modifying the function of a gene.

Learning Objectives

- Describe the utility of experimentally introduced Transposons

Key Points

- Transposons contain signals to truncate expression of an interrupted gene, thus inactivating it.
- Transposons are widely used tools in biology, frequently utilized for insertion mutagenesis, large-scale gene disruption studies, and gene tagging.
- Transposon-mediated gene disruption experiments and promoter traps rely on promiscuous, undirected, and pseudo-random insertion of the transposon.

Key Terms

- **transposable**: Able to be transposed (in any sense).
- **plasmid**: A circle of double-stranded DNA that is separate from the chromosomes, which is found in bacteria and protozoa.

A transposable element (TE) is a DNA sequence that can change its relative position (self-transpose) within the genome of a single cell. The mechanism of transposition can be either "copy and paste" or "cut and paste. " Transposition can create phenotypically significant mutations and alter the cell's genome size. Barbara McClintock's discovery of these jumping genes early in her career earned her a Nobel prize in 1983.

Transposons in bacteria usually carry an additional gene for function other than transposition—often for antibiotic resistance. In bacteria, transposons can jump from chromosomal DNA to plasmid DNA and back, allowing for the transfer and permanent addition of genes such as those encoding antibiotic resistance (multi-antibiotic resistant bacterial strains can be generated in this way). When the transposable elements lack additional genes, they are known as insertion sequences. Transposons are semi-parasitic DNA sequences that can replicate and spread through the host 's genome. They can be harnessed as a genetic tool for analysis of gene and protein function. The use of transposons is well-developed in Drosophila (in which P elements are most commonly used) and in Thale cress (Arabidopsis thaliana) and bacteria such as Escherichia coli (E. coli).

Synthetic DNA transposon system are constructed to introduce precisely defined DNA sequences into the chromosomes of vertebrate animals for the purposes of introducing new traits and to discover new genes and their functions (e.g. by establishing a loss-of-function phenotype or gene inactivation). Transposition is a precise process in which a defined DNA segment is excised from one DNA molecule and moved to another site in the same or different DNA molecule or genome.

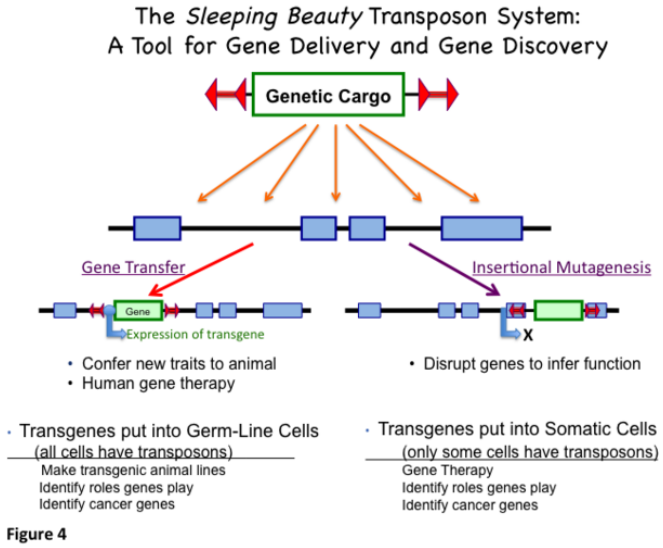

Figure: **Transposon System**: The sleeping beauty transposon system applications.

Insertional inactivation is a technique used in recombinant DNA engineering where a plasmid (such as pBR322) is used to disable the expression of a gene. A gene is inactivated by inserting a fragment of DNA into the middle of its coding sequence. Any future products from the inactivated gene will not work because of the extra codes added to it. An example is the use of pBR322, which has genes that respectively encode polypeptides that confer resistance to ampicillin and tetracyclin antibiotics. As a result, when a genetic region is interrupted by integration of pBR322, the gene function is lost but new gene function (resistance to specific antibiotics) is gained. An alternative strategy for insertional mutagenesis has been used in vertebrate animals to find genes that cause cancer. In this case a transposon, e.g. Sleeping Beauty, is designed to interrupt a gene in such a way that it causes maximal genetic havoc. Specifically, the transposon contains signals to truncate expression of an interrupted gene at the site of the insertion and then restart expression of a second truncated gene. This method has been used to identify oncogenes.

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7.25B: DNA Sequencing of Insertion Sites

An insertion site is the position at which a transposable genetic element is integrated.

Learning Objectives

- Discuss the uses of sequencing insertions sites

Key Points

- Several methods exist to analyze insertion sequences, including inverse polymerase chain reaction. The inverse PCR involves a series of restriction digests and ligation, resulting in a looped fragment that can be primed for PCR from a single section of known sequence.
- The amplified product can then be sequenced and compared with DNA databases to locate the sequence which has been disrupted.
- Other techniques include Southern hybridization and modifications of the PCR protocol.

Key Terms

- **transposons**: A segment of DNA that can move to a different position within a genome.

An insertion sequence (also known as an IS, an insertion sequence element, or an IS element) is a short DNA sequence that acts as a simple transposable element.

Insertion sequences have two major characteristics: they are small relative to other transposable elements (generally around 700 to 2500 bp in length) and only code for proteins implicated in the transposition activity (they are thus different from other transposons, which also carry accessory genes such as antibiotic-resistance genes).

These proteins are usually the transposase which catalyse the enzymatic reaction allowing the IS to move, and also one regulatory protein which either stimulates or inhibits the transposition activity. The coding region in an insertion sequence is usually flanked by inverted repeats. For example, the well-known IS911 (1250 bp) is flanked by two 36bp inverted repeat extremities and the coding region has two genes partially overlapping orfA and orfAB, coding the transposase (OrfAB) and a regulatory protein (OrfA).

A particular insertion sequence may be named according to the form ISn, where n is a number (e.g. IS1, IS2, IS3, IS10, IS50, IS911, IS26, etc.); this is not the only naming scheme used, however. Although insertion sequences are usually discussed in the context of prokaryotic genomes, certain eukaryotic DNA sequences belonging to the family of Tc1/mariner transposable elements may be considered to be insertion sequences.

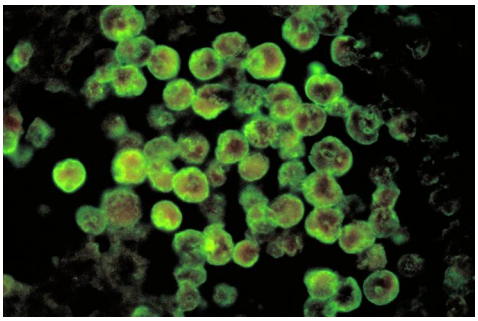

Figure: **Naegleria fowleri**: Antibody detection (green) of Naegleria fowleri, the organism responsible for Primary amoebic meningoencephalitis (PAM).

In addition to occurring autonomously, insertion sequences may also occur as parts of composite transposons; in a composite transposon, two insertion sequences flank one or more accessory genes, such as an antibiotic-resistance gene (e.g. Tn10, Tn5). Nevertheless, there exist another sort of transposons, called unit transposons, that do not carry insertion sequences at their extremities (e.g. Tn7). A complex transposon does not rely on flanking insertion sequences for resolvase. The resolvase is part of the tns genome and cuts at flanking inverted repeats.

Although several methods are available for locating ISs in microbial genomes, they are either labor intensive or inefficient. These include Southern hybridization, inverse Polymerase Chain Reaction (iPCR), and most recently, vectorette PCR to identify and map

the genomic positions of the insertion sequences.

Southern hybridization is rather time-consuming and requires additional procedures for localizing ISs. Inverse PCR, a commonly-used PCR method for recovering unknown flanking sequences of a known target sequence, uses a library of circularized chromosomal DNA fragments as a template and two outward primers located in each end of the known fragment for amplification. However, when a target sequence has multiple genomic locations, the variously-sized DNA circles formed are difficult to amplify simultaneously. Also, the length of each restriction DNA fragment containing a target sequence must be determined by Southern hybridization followed by sub-genomic fractioning before intramolecular ligation and PCR amplification. These difficulties render Southern hybridization and iPCR impractical as techniques for quickly surveying repetitive elements in genomes.

Vectorette PCR (vPCR) is another method used to amplify unknown sequences flanking a characterized DNA fragment. It involves cutting genomic DNAs with a restriction enzyme, ligating vectorettes to the ends, and amplifying the flanking sequences of a known sequence using primers derived from the known sequence along with a vectorette primer.

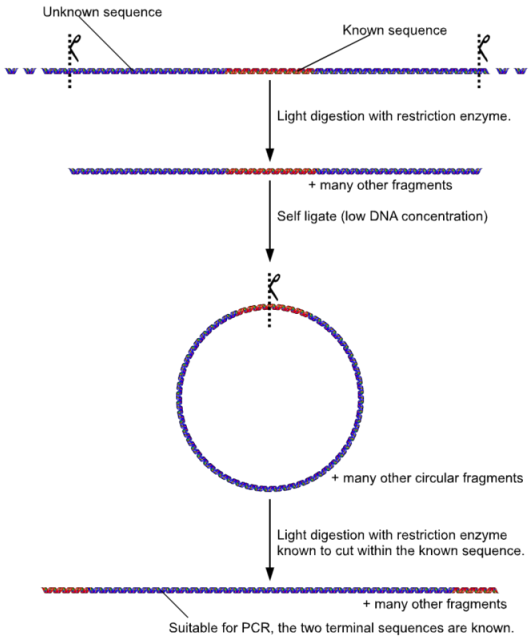

Figure: **Inverse PCR**: Summary of iPCR process

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7.25C: Northern Blots

Northern blots allow investigators to determine messenger RNA molecular weight and sample content.

Learning Objectives

- Evaluate the applications of Northern Blots

Key Points

- RNA (either total RNA or just mRNA) is separated by gel electrophoresis, usually an agarose gel. Because there are so many different RNA molecules on the gel, it usually appears as a smear rather than discrete bands.
- The RNA is transfered to a sheet of special blotting paper called nitrocellulose, though other types of paper, or membranes, can be used. The RNA molecules retain the same pattern of separation they had on the gel.
- The blot is incubated with a probe which is single-stranded DNA. This probe will form base pairs with its complementary RNA sequence and bind to form a double-stranded RNA-DNA molecule. The probe is either radioactive or has an enzyme bound to it.

Key Terms

- **hybridization**: The act of hybridizing, or the state of being hybridized.

The Northern blot is a technique used in molecular biology research to study gene expression in a sample, through detection of RNA (or isolated messenger RNA). With Northern blotting it is possible to observe cellular control over structure and function by determining the particular gene expression levels during differentiation, morphogenesis, as well as abnormal or diseased conditions. Northern blotting involves the use of electrophoresis to separate RNA samples by size and detection with a hybridization probe complementary to part of or the entire target sequence.

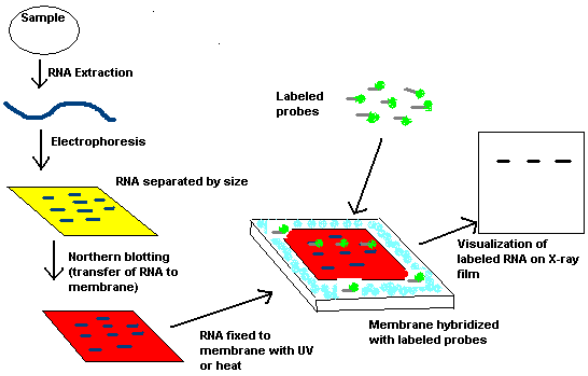

Figure: **Northern blot technique**: Flow diagram outlining the general procedure for RNA detection by northern blotting.

The term ‘Northern blot’ actually refers specifically to the capillary transfer of RNA from the electrophoresis gel to the blotting membrane. However, the *entire* process is commonly referred to as Northern blotting. The northern blot technique was developed in 1977 by James Alwine, David Kemp, and George Stark at Stanford University. Northern blotting takes its name from its similarity to the first blotting technique, the Southern blot, named for biologist Edwin Southern. The major difference is that RNA, rather than DNA, is analyzed in the Northern blot.

A general blotting procedure starts with extraction of total RNA from a homogenized tissue sample or from cells. Eukaryotic mRNA can then be isolated through the use of oligo (dT) cellulose chromatography to isolate only those RNAs with a poly(A) tail. RNA samples are then separated by gel electrophoresis. Since the gels are fragile and the probes are unable to enter the matrix, the RNA samples, now separated by size, are transferred to a nylon membrane through a capillary or vacuum blotting system.

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7.25D: Western Bolts

Learning Objectives

- Show the uses of Western Blots

The Western blot (sometimes called the protein immunoblot) is a widely accepted analytical technique used to detect specific proteins in a given sample of tissue homogenate or extract. Western blot samples can be taken from whole tissue or from cell culture. Solid tissues are first broken down mechanically using either a blender (for larger sample volumes), a homogenizer (smaller volumes), or by sonication. Assorted detergents, salts, and buffers may be employed to encourage lysis of cells and to solubilize proteins. The technique uses gel electrophoresis to separate native proteins by 3-D structure or denatured proteins by the length of the polypeptide.

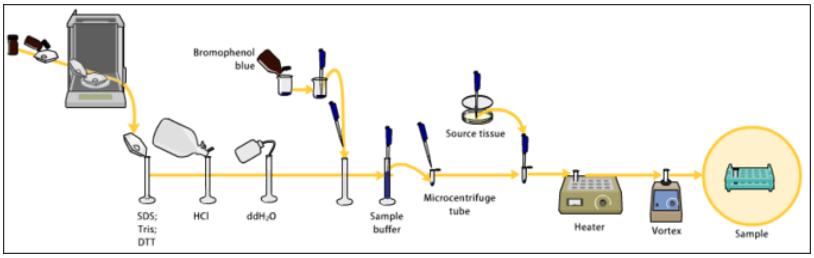

Figure: ***Western blot steps****: Example preparation to use in the Western blot technique.*

The proteins are then transferred to a membrane (typically nitrocellulose or PVDF), where they are stained with antibodies specific to the target protein. There are now many reagent companies that specialize in providing antibodies (both monoclonal and polyclonal antibodies) against tens of thousands of different proteins belonging to signaling pathways or cell surface receptor antigens, or other cellular or soluble components. Commercial antibodies can be expensive, although the unbound antibody can be reused between experiments. This method is used in the fields of molecular biology, biochemistry, immunogenetics and other molecular biology disciplines. Other related techniques include using antibodies to detect proteins in tissues and cells by immunostaining and enzyme-linked immunosorbent assay (ELISA). This method originated in the laboratory of George Stark at Stanford. The name Western blot was given to the technique by W. Neal Burnette and is a play on the name Southern blot, a technique for DNA detection developed earlier by Edwin Southern. Detection of RNA is termed Northern blot.

Key Points

- After separation by gel electrophoresis using SDS-PAGE, proteins are transfered to a sheet of special blotting paper called nitrocellulose, though other types of paper, or membranes, can be used. The proteins retain the same pattern of separation they had on the gel.
- The blot is incubated with a generic protein (such as milk proteins) to bind to any remaining sticky places on the nitrocellulose. An antibody is then added to the solution which is able to bind to its specific protein. The antibody is conjugated to alkaline phosphatase or horseradish peroxidase.
- The location of the antibody is revealed by incubating it with a colorless substrate that the attached enzyme converts to a colored product that can be seen and photographed.

Key Terms

- **electrophoresis**: a method for the separation and analysis of large molecules (such as proteins) by migrating a colloidal solution of them through a gel; gel electrophoresis

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7.25E: DNA Mobility Shifts

DNA mobility shift assay is a technique for studying gene regulation and determining protein-DNA interactions.

Learning Objectives

- Identify the utility of DNA mobility shift assays

Key Points

- The interaction of proteins with DNA is central to the control of many cellular processes, including DNA replication, recombination and repair, transcription, and viral assembly.
- An advantage of studying protein-DNA interactions by an electrophoretic mobility shift assay is the ability to resolve complexes of different stoichiometry or conformation.
- The source of the DNA-binding protein may be a crude nuclear or whole cell extract, in vitro transcription product, or a purified preparation.

Key Terms

- **polyacrylamide**: Any of a range of cross-linked polymers of acrylamide; used to form soft gels.

A mobility shift assay is electrophoretic separation of a protein-DNA or protein- RNA mixture on a polyacrylamide or agarose gel for a short period. The speed at which different molecules (and combinations thereof) move through the gel is determined by their size and charge, and to a lesser extent, their shape. The control lane (a DNA probe without protein present) will contain a single band corresponding to the unbound DNA or RNA fragment. However, assuming that the protein is capable of binding to the fragment, the lane with protein present will contain another band that represents the larger, less mobile, complex of nucleic acid probe bound to protein, which is “shifted” up on the gel (since it has moved more slowly).

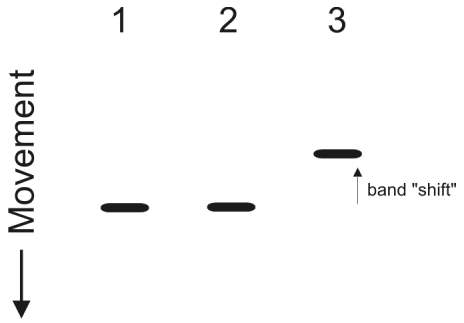

Figure: **Gel Shift Assay**: Lane 1 is a negative control, and contains only DNA. Lane 2 contains protein as well as a DNA fragment that, based on its sequence, does not interact. Lane 3 contains protein and a DNA fragment that does react; the resulting complex is larger, heavier, and slower-moving. The pattern shown in lane 3 is the one that would result if all the DNA were bound and no dissociation of complex occurred during electrophoresis. When these conditions are not met a second band might be seen in lane 3 reflecting the presence of free DNA or the dissociation of the DNA-protein complex.

Under the correct experimental conditions, the interaction between the DNA and protein is stabilized and the ratio of bound to unbound nucleic acid on the gel reflects the fraction of free and bound probe molecules as the binding reaction enters the gel. This stability is in part due to the low ionic strength of the buffer, but also due to a “caging effect”; the protein, surrounded by the gel matrix, is unable to diffuse away from the probe before they recombine. If the starting concentrations of protein and probe are known, and if the stoichiometry of the complex is known, the apparent affinity of the protein for the nucleic acid sequence may be determined. An antibody that recognizes the protein can be added to this mixture to create an even larger complex with a greater shift. This method is referred to as a supershift assay, and is used to unambiguously identify a protein present in the protein-nucleic acid complex.

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7.25F: Purifying Proteins by Affinity Tag

Protein tags are peptide sequences genetically grafted onto a recombinant protein.

Learning Objectives

- Indicate the uses of protein affinity tags

Key Points

- Affinity tags are appended to proteins so that they can be purified from their crude biological source using an affinity technique.
- Recombinant proteins that carry small affinity tags are efficiently expressed in bacteria, insect, or mammalian cells.
- After cell lysis and clearing of the lysate, tagged proteins are purified using an immobilized-metal affinity chromatography procedure.

Key Terms

- **protein**: Proteins are large biological molecules consisting of one or more chains of amino acids.
- **affinity**: An attractive force between atoms, or groups of atoms, that contributes toward their forming bonds.
- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.

Protein tags are peptide sequences genetically grafted onto a recombinant protein. Often these tags are removable by chemical agents or by enzymatic means, such as proteolysis or intein splicing. Tags are attached to proteins for various purposes.

Affinity tags are appended to proteins so that they can be purified from their crude biological source using an affinity technique. These include chitin binding protein (CBP), maltose binding protein (MBP), and glutathione-S-transferase (GST). The poly (His) tag is a widely-used protein tag; it binds to metal matrices.

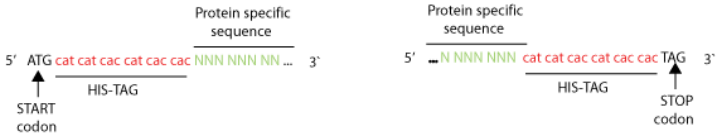

Figure: **Adding Polyhistidine Tags**: This is an example of a primer designed to add a 6xHis-tag using PCR. Eighteen bases coding six histidines are inserted right after the START codon or right before the STOP codon. At least 16 bases specific to the gene of interest are needed next to the His-tag. With 6 His, the protein will have an added 1 kDa of molecular weight. Oftentimes, a linker (such as gly-gly-gly or gly-ser-gly) is placed between the protein of interest and the 6 His tag. This is to prevent the polyhistidine tag from affecting the activity of the protein being tagged.

Solubilization tags are used, especially for recombinant proteins expressed in chaperone-deficient species such as E. coli, so as to assist in the proper folding in proteins and keep them from precipitating. These include thioredoxin (TRX) and poly (NANP). Some affinity tags have a dual role as a solubilization agent, such as MBP and GST.

Chromatography tags are used to alter chromatographic properties of the protein to afford different resolution across a particular separation technique. These often consist of polyanionic amino acids, such as FLAG-tag.

Epitope tags are short peptide sequences which are chosen because high-affinity antibodies can be reliably produced in many different species. These are usually derived from viral genes, which explain their high immunoreactivity. Epitope tags include V5-tag, c-myc-tag, and HA-tag. These tags are particularly useful for western blotting, immunofluorescence and immunoprecipitation experiments, although they also find use in antibody purification.

Fluorescence tags are used to give visual readout on a protein. GFP and its variants are the most commonly used fluorescence tags. More advanced applications of GFP include using it as a folding reporter (fluorescent if folded, colorless if not).

Protein tags are also useful for specific enzymatic modification (such as biotin ligase tags) and chemical modification (FlAsH) tag. Often tags are combined to produce multifunctional modifications of the protein. However, with the addition of each tag comes the risk that the native function of the protein may be abolished or compromised by interactions with the tag.

Examples of peptide tags include:

- AviTag, a peptide allowing biotinylation by the enzyme BirA and so the protein can be isolated by streptavidin (GLNDIFEAQKIEWHE)

- Calmodulin-tag, a peptide bound by the protein calmodulin (KRRWKKNFIAVSAANRFKKISSSGAL)
- FLAG-tag, a peptide recognized by an antibody (DYKDDDDK)
- HA-tag, a peptide recognized by an antibody (YPYDVPDYA)
- His-tag, 5-10 histidines bound by a nickel or cobalt chelate (HHHHHH)
- Myc-tag, a short peptide recognized by an antibody (EQKLISEEDL)
- S-tag (KETAAAKFERQHMDS)
- SBP-tag, a peptide which binds to streptavidin (MDEKTTGWRGGHVVEGLAGELEQLRARLEHHPQGQREP)
- Softag 1, for mammalian expression (SLAELLNAGLGGS)
- Softag 3, for prokaryotic expression (TQDPSRVG)
- V5 tag, a peptide recognized by an antibody (GKPIPNPLLGLDST)
- Xpress tag (DLYDDDDK)

Examples of protein tags include:

- BCCP (Biotin Carboxyl Carrier Protein), a protein domain recognized by streptavidin
- Glutathione-S-transferase-tag, a protein which binds to immobilized glutathione
- Green fluorescent protein-tag, a protein which is spontaneously fluorescent and can be bound by nanobodies
- Maltose binding protein-tag, a protein which binds to amylose agarose
- Nus-tag
- Strep-tag, a peptide which binds to streptavidin or the modified streptavidin called streptactin (Strep-tag II: WSHPQFEK)
- Thioredoxin-tag

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7.25G: Primer Extension Analysis

Primer extension is used to map the 5′ ends of DNA or RNA fragments.

LEARNING OBJECTIVES

Outline primer extension analysis

KEY TAKEAWAYS

Key Points

- Primer extension assay is done by annealing a specific oligonucleotide primer to a position downstream of that 5′ end.
- The primer is radiolabelled, usually at its 5′ end. This is extended with reverse transcriptase, which can copy either an RNA or a DNA template, making a fragment that ends at the 5′ end of the template molecule.
- Primer extension analysis includes selection and preparation of a labeled primer complementary to the RNA transcript of interest; hybridization of the primer to a region of the RNA under study; extension from the primer by an RNA-dependent DNA polymerase to synthesize a cDNA strand.
- Analysis of primer extension of the extended cDNA products is done on denaturing polyacrylaminde gels and autoradiography.

Key Terms

- **radiolabelled**: Tagged with a radiotracer.
- **polyacrylamide**: Any of a range of cross-linked polymers of acrylamide; used to form soft gels.

Primer Extension Analysis

Primer extension is a technique whereby the 5′ ends of RNA or DNA can be mapped. Primer extension can be used to determine the start site of RNA transcription for a known gene. This technique requires a radiolabelled primer (usually 20 to 50 nucleotides in length) which is complementary to a region near the 3′ end of the gene. The primer is allowed to anneal to the RNA and reverse transcriptase is used to synthesize cDNA from the RNA until it reaches the 5′ end of the RNA. By running the product on a polyacrylamide gel, it is possible to determine the transcriptional start site, as the length of the sequence on the gel represents the distance from the start site to the radiolabelled primer.

Applications of Primer Extension Analysis

Primer extension analysis has three main applications. First, it is used for mapping the 5′ end of transcripts. This allows one to determine the transcription initiation site (assuming the mRNA isn't further processed), which helps localize promoters or TATA boxes. Second, it can be used to quantify the amount of transcript in an in vitro transcription system.

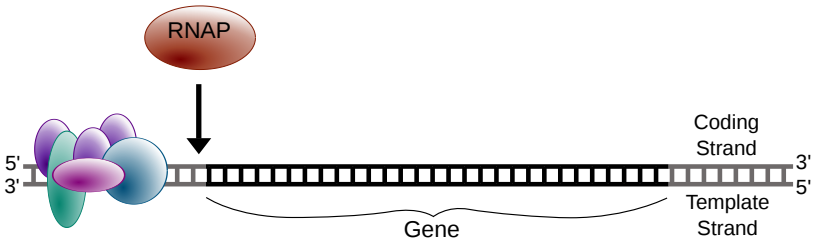

Figure: **Transcription initiation site**: This is a diagram of transcription initiation by the RNA polymerase.

Third, it can be used to determine the locations of breaks or modified bases in a mixed population of RNA or DNA samples. This is useful in applications like footprinting. Two different methods are used. In one, the modified nucleotide cannot be recognized by the polymerase or reverse transcriptase; in such cases, the chain ends at the site of modification. In the other, the modification is converted in a later step of the analysis to a strand break by chemical treatment. For instance, the sites of modifications by dimethyl sulfate (DMS) can be identified by treating DNA with DMS, exposing the sample to conditions that break the backbone at the site of modification, followed by primer extension.

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7.25H: DNA Protection Analysis

DNA protection or “footprinting” analysis is a powerful technique for identifying the nucleotides involved in a protein-DNA interaction.

LEARNING OBJECTIVES

Illustrate DNA protection analysis

KEY TAKEAWAYS

Key Points

- DNA protection analysis is a technique in which a DNA molecule is ‘incubated’ with a protein that binds to a specific site along the double helix.
- The DNA-binding protein complex is then subjected to restriction endonuclease digestion, which reduces the entire DNA to mono- and oligonucleotide fragments, except for the portion of the DNA molecule that was ‘protected’ from digestion by the binding protein.
- Removal of the protein by simple chemical means—e.g., by gel electrophoresis —allows the study of DNA and binding protein interaction.

Key Terms

- **electrophoresis**: a method for the separation and analysis of large molecules (such as proteins) by migrating a colloidal solution of them through a gel; gel electrophoresis
- **polymerase chain reaction**: A technique in molecular biology for creating multiple copies of DNA from a sample; used in genetic fingerprinting etc.

DNA protection or footprinting is a technique from molecular biology/biochemistry that detects DNA-protein interaction using the fact that a protein bound to DNA will often protect that DNA from enzymatic cleavage. This makes it possible to locate a protein binding site on a particular DNA molecule. The method uses an enzyme, deoxyribonuclease (DNase, for short) to cut the radioactively end-labeled DNA, followed by gel electrophoresis to detect the resulting cleavage pattern. For example, the DNA fragment of interest may be amplified by polymerase chain reaction, with the result being many DNA molecules with a radioactive label on one end of one strand of each double stranded molecule. Cleavage by DNase will produce fragments, the smaller of which will move further on the electrophoretic gel.

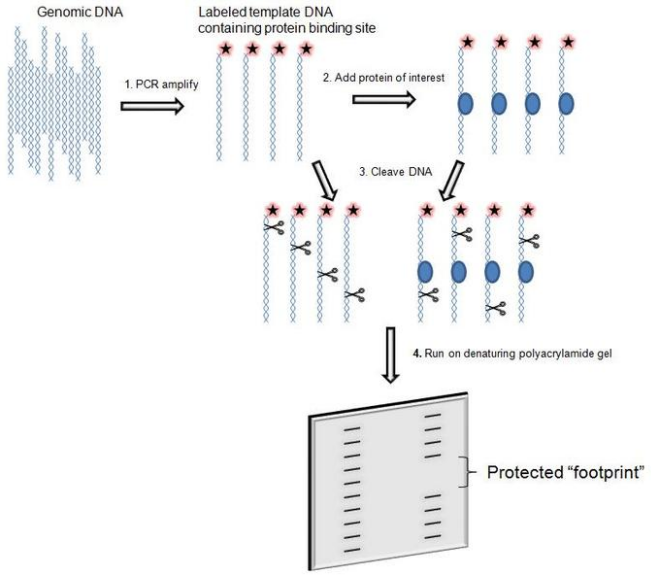

Figure: **DNA footprinting**: DNA protection or footprinting technique

The fragments which are smaller will appear further on the gel than the longer fragments. The gel is then used to expose a special photographic film. The cleavage pattern of the DNA in the absence of a DNA binding protein, typically referred to as free DNA, is

compared to the cleavage pattern of DNA in the presence of a DNA binding protein. If the protein binds DNA, the binding site is protected from enzymatic cleavage. This protection will result in a clear area on the gel which is referred to as the “footprint”. By varying the concentration of the DNA-binding protein, the binding affinity of the protein can be estimated according to the minimum concentration of protein at which a footprint is observed. This technique was developed by David Galas and Albert Schmitz at Geneva in 1977.

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7.25I: Whole-Genome DNA-Binding Analysis

Whole-genome DNA-binding analysis is a powerful tool for analyzing epigenetic modifications and DNA sequences bound to regulatory proteins.

LEARNING OBJECTIVES

Describe whole-genome DNA-binding analysis

KEY TAKEAWAYS

Key Points

- Whole-genome DNA binding analysis, also known as location analysis, utilizes chromatin immunoprecipitation and microarray chip.
- Whole-genome DNA-binding analysis utilizes ChIP-on-chip method. Briefly, protein -DNA complexes are crosslinked, immunoprecipitated, purified, amplified and labeled, and then allowed to hybridize to a variety of high-resolution arrays.
- This technique is a high-throughput (genome-wide) identification and analysis of DNA fragments that are bound by specific proteins such as histones, and transcriptional factors.

Key Terms

- **immunoprecipitation**: A technique in which an antigen is precipitated from a solution by using an antibody, or a particular use of this technique.

Genomic DNA sequences are being determined at an increasingly rapid pace. This has created a need for more efficient techniques to determine which parts of these sequences are bound in-vivo by the proteins controlling processes; such as gene expression, DNA replication and chromosomal mechanics.

A whole-genome approach was established to identify and characterize such DNA sequences. The method of chromatin immunoprecipitation, combined with microarrays (ChIP-Chip), is a powerful tool for genome-wide analysis of protein binding. It has also become a widely-used method for genome-wide localization of protein-DNA interactions.

The first step in the ChIP-Chip procedure is to fix protein-DNA interactions in living cells by chemical crosslinking. The crosslinker must be small to diffuse fast into the cells. In practice, formaldehyde is used in most ChIP-Chip experiments. After cell lysis, the DNA is fragmented by sonication. This extract is then subjected to immunoprecipitation (IP) with a specific antibody against the protein of interest.

DNA bound by the protein will be coprecipitated and enriched, compared to DNA not bound by the respective protein. To facilitate immunoprecipitation and subsequent washing, antibodies are usually coupled to either agarose- or magnetic beads via protein A or G. After reversion of crosslinking, the DNA is purified by phenol extraction or commercial polymerase chain reaction (PCR) cleanup kits.

Often, an amplification step is included after DNA purification. Two different fluorescence labels are used to label the IP DNA, and a hybridization -control DNA, respectively. Usually, total DNA before IP (input DNA) is used as hybridization control.

The two differentially-labeled DNAs are hybridized to the same microarray and the difference in fluorescence intensity gives a measure of the enrichment.

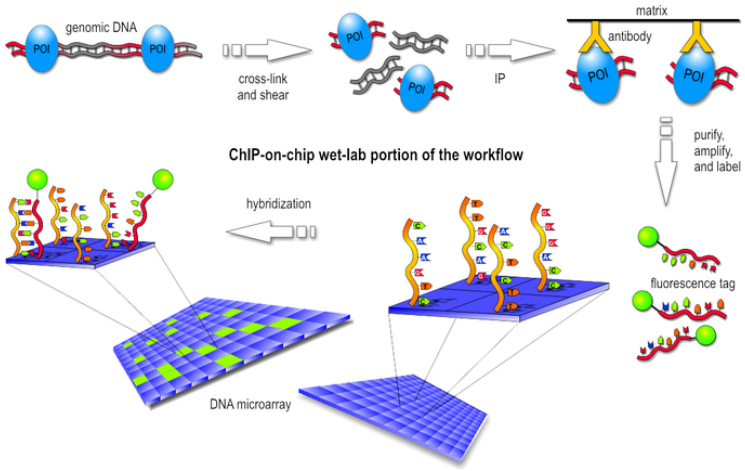

Figure: **ChIP-chip procedure**: ChIP-chip workflow performed in laboratory

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7.25J: Two-Hybrid Analysis

Learning Objectives

- Design a two-hybrid experiment

Understanding how proteins are physically connected reveals clues about their structure, function, and makes them an ideal target for drug therapy. Several methodologies exist to study the interaction of proteins in vivo. The most widely employed tools are the yeast two-hybrid system. The yeast two-hybrid screening system is an effective and quick tool for the in vivo study of protein–protein interaction both in prokaryotes and eukaryotes. The method consists of splitting a yeast transcription factor into its binding domain and activation domain, fusing the binding domain to one protein of interest (the bait) and the activation domain to another protein of interest (the prey), and reconstituting the activity of the transcription factor by bringing the two domains back into physical proximity. In the absence of an interaction the domains remain distant, preventing a detectable output. If the two proteins do interact the bait recruits the prey to a specific cellular location where it can stimulate a detectable output (e.g., gene activation). This experimental approach measures direct physical interaction between proteins and is called a binary method. Datasets obtained from such tools are further analyzed using computational methods to draw a map of protein connectivity and achieve system level understanding of a microorganism.

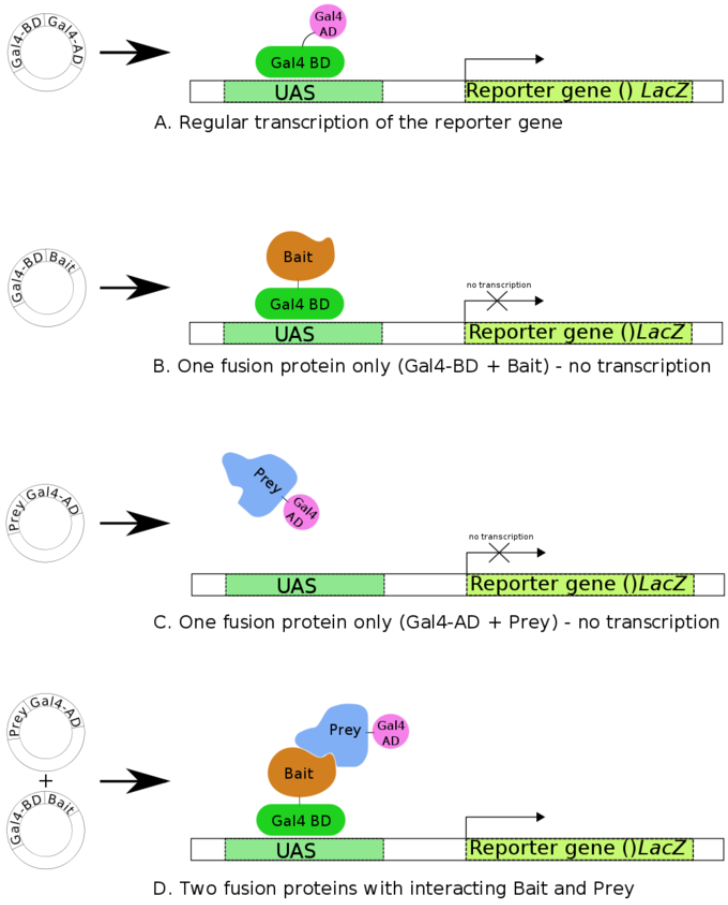

Figure: **Two-hybrid technique**: Overview of two-hybrid assay, checking for interactions between two proteins, called here Bait and Prey.

One limitation of classic yeast two-hybrid screens is that they are limited to soluble proteins. It is therefore impossible to use them to study the protein–protein interactions between insoluble integral membrane proteins. The split- ubiquitin system provides a method for overcoming this limitation. In the split-ubiquitin system, two integral membrane proteins to be studied are fused to two different ubiquitin moieties: a C-terminal ubiquitin moiety (“Cub”, residues 35–76) and an N-terminal ubiquitin moiety (“Nub”, residues 1–34). These fused proteins are called the bait and prey, respectively. In addition to being fused to an integral membrane protein, the Cub moiety is also fused to a transcription factor (TF) that can be cleaved off by ubiquitin specific proteases. Upon

bait–prey interaction, Nub and Cub-moieties assemble, reconstituting the split-ubiquitin. The reconstituted split-ubiquitin molecule is recognized by ubiquitin specific proteases, which cleave off the reporter protein, allowing it to induce the transcription of reporter genes.

Summary

A key part of gene functional analysis and potential drug target discovery is an understanding of how proteins interact within the cell. Commercially available products facilitate the characterization of these interactions in yeast systems. The basic format involves the creation of two hybrid molecules, one in which a “bait” protein is fused with a transcription factor, and one in which a “prey” protein is fused with a related transcription factor. If the bait and prey proteins indeed interact, then the two factors fused to these two proteins are also brought into proximity with each other.

Key Terms

- **computational**: Of or relating to computation.
- **ubiquitin**: A small regulatory protein sequence that directs proteins to specific compartments within the cell. Specifically, a ubiquitin tag directs the protein to a proteasome, which destroys and recycles the components.

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SECTION OVERVIEW

7.26: Cell Physiology Techniques

Topic hierarchy

7.26A: Mapping Protein-Protein Interactions

7.26D: Phase Display

7. 26B: Tracking Cells with Light

7. 26C: Multiplex and Real-Time PCR

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7.26A: Mapping Protein-Protein Interactions

Learning Objectives

- Compare techniques used for mapping protein-protein interactions

In living organisms most of the biological functions are mediated by complex multi-component protein machineries and network activities. The protein complexes formed could be stable (proteins interact for a prolonged period of time) or transient (proteins interact for a brief period of time). Molecular studies are necessary to dissect the constituents of these protein complexes and identify the domains through which a protein interacts with another. Understanding how proteins are physically connected reveals clues about their structure and function and makes them an ideal target for drug therapy. Several methodologies exist to study the interaction of proteins *in vivo*. The most widely employed tools are the yeast two-hybrid system and affinity purification coupled to mass spectrometry. Datasets obtained from such tools are further analyzed using computational methods to draw a map of protein connectivity and achieve system level understanding of a microorganism. The complete map of protein interactions that can occur in a living organism is called the interactome.

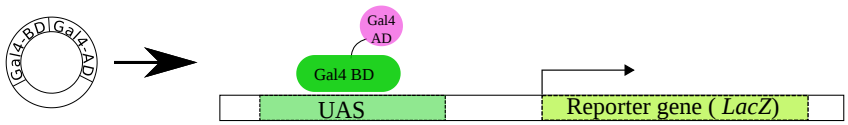
The Yeast Two-hybrid System

The yeast two-hybrid screening system is an effective and quick tool for the in vivo study of protein–protein interaction both in prokaryotes and eukaryotes. The method consists of splitting a yeast transcription factor into its binding domain and activation domain, fusing the binding domain to one protein of interest (the bait) and the activation domain to another protein of interest (the prey), and reconstituting the activity of the transcription factor by bringing the two domains back into physical proximity. In the absence of an interaction the domains remain distant, preventing a detectable output. If the two proteins do interact the bait recruits the prey to a specific cellular location where it can stimulate a detectable output (e.g., gene activation). This experimental approach measures direct physical interaction between proteins and is called a binary method.

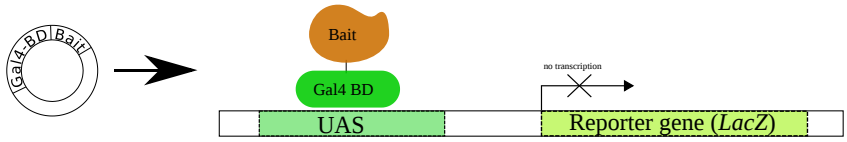
Affinity Purification Coupled to Mass Spectrometry

Affinity purification of protein complexes coupled to mass spectrometry is carried out as follows: a specific protein (the bait) is manipulated to express an affinity tag. The tag serves as a tool to purify the bait protein and associated proteins by affinity chromatography. Purified protein complexes are then resolved on native gels and discrete protein bands are excised and digested into small peptide fragments by trypsin.

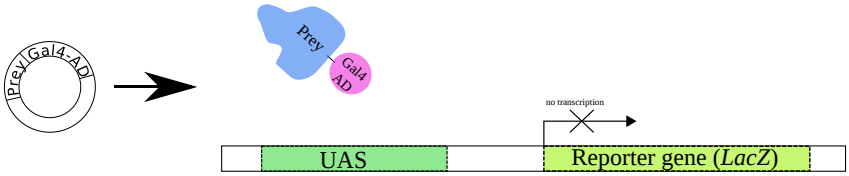
Peptides are identified using mass spectrometry methods. The identity of the protein associated with a given bait protein is determined by comparing its peptide fingerprint against available databases. This method allows for the identification and quantification of direct binding partners and secondary interacting proteins, and assigns them into protein networks. This experimental approach measures physical interactions between groups of proteins without distinguishing whether they are direct or indirect and is termed co-complex method. Results collected from binary and co-complex experiments are documented into a database. There are many databases accessible online that allow for protein clustering by function and nature of interaction and provide a rich framework for biomedical research.



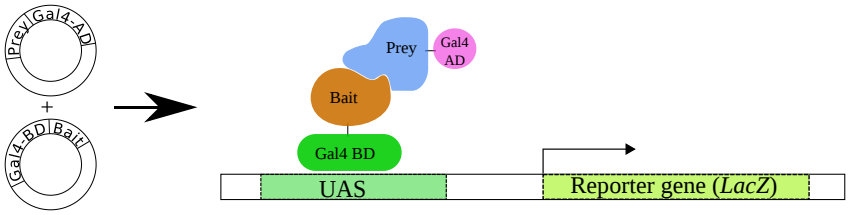
A. Regular transcription of the reporter gene



B. One fusion protein only (Gal4-BD + Bait) - no transcription



C. One fusion protein only (Gal4-AD + Prey) - no transcription



D. Two fusion proteins with interacting Bait and Prey

Figure: ***The Yeast two-hybrid method***: *Principle of the bait and prey method for the study of protein-protein interaction.*

Key Points

- A key question about a protein, in addition to when and where it is expressed, is with which other proteins does it interact?
- Interaction partners are an immediate lead into biological function and can potentially be exploited for therapeutic purposes.
- Creation of a protein–protein interaction map of the cell would be of immense value to understanding the biology of the cell.
- The most common approaches used to identify protein-protein interactions are the yeast two-hybrid system and affinity purification coupled to mass spectrometry.

Key Terms

- **Affinity chromatography**: Method of separating a biochemical mixture based on highly specific interactions.
- **mass spectrometry**: Analytical method that allows ionizing molecules and sorting them according to their mass and charge.

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7.26D: Phase Display

Learning Objectives

- Assess the uses of phage display technology

A phage or bacteriophage is a virus capable of infecting a bacterial cell, and may cause lysis to its host cell. Bacteriophages have a specific affinity for bacteria. They are made of an outer protein coat or capsid that encloses the genetic material (which can be RNA or DNA, about 5,000 to 500,000 nucleotides in length). They inject their genetic material into the bacterium following infection. When the strain is virulent, all the synthesis of the host's DNA, RNA and proteins ceases. The phage genome is then used to direct the synthesis of phage nucleic acids and proteins using the host's transcriptional and translational apparatus. When the sub-components of the phage are produced, they self-assemble to form new phage particles. The new phages produce lysozyme that ruptures the cell wall of the host, leading to the release of the new phages, each ready to invade other bacterial cells. This inherent property of phages is the basis for the phage display technology.

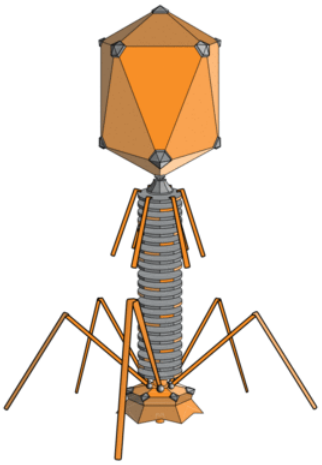

Figure: ***Bacteriophage****: A bacteriophage is a virus that infects bacteria.*

Phage display technology is the process of inserting new genetic material into a phage gene. The bacteria process the new gene so that a new protein or peptide is made. This protein or peptide is exposed on the phage surface. Phage display begins by inserting a diverse set of genes into the phage genome with each phage receiving a different gene. The modified gene contains an added segment (an antibody, small protein, or peptide), which is to be expressed on the surface of the phage. Each phage receives only one gene, so each expresses a single protein or peptide. A collection of phage displaying a population of related but diverse proteins or peptides is called a library. The related proteins keep most of the physical and chemical properties of their parent protein. The library is then exposed to an immobilized target. It is anticipated that some members of the library will bind to the target through an interaction between the displayed molecule and the target itself. After the phage is given the chance to bind to a target, the immobilized target is washed to remove phage that did not bind. Replicating the bound phage in bacteria increases the amount of phage several million-fold overnight, providing enough material for sequencing. Sequencing of the phage DNA tells the identity of the peptide that binds the target. Phage libraries are screened for binding to synthetic or native targets.

Phage display technology is advantageous in many applications including selection of inhibitors for the active and allosteric sites of enzymes, receptor agonists and antagonists, and G-protein binding modulatory peptides. Phage display is also used in epitope mapping and analysis of protein-protein interactions. The specific molecules isolated from phage libraries can be used in therapeutic target validation, drug design and vaccine development.

Key Points

- A phage, short for bacteriophage, is a virus that reproduces itself in bacteria.
- Phage display technology introduces genes into the phage's genome which encoded proteins would be presented on the surface of the phage.
- Displayed proteins are tested for binding affinity against target molecules immobilized on a platform.

Key Terms

- **lysozyme**: enzyme that damages bacterial cell wall.
- **sequencing**: the process of reading the nucleotide bases in a DNA molecule.

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7. 26B: Tracking Cells with Light

Advanced technology enables tracking cells with light by introducing fluorescent or luminescent reporter genes into the cells' genome.

LEARNING OBJECTIVES

Compare the ways light can used to track cells

KEY TAKEAWAYS

Key Points

- The ability of tracking cells with light has revolutionized molecular biology and provided means to study biological processes as they happen.
- The most common tools used to illuminate a cell are fluorescent (GFP) and luminescent (luciferase) reporter genes.
- Reporter genes are introduced into the host 's genome and are controlled by the regulatory sequence of the gene under investigation (gene X). Thus when gene X is expressed it will drive along the expression of the reporter gene and the cell will fluoresce or emit light.
- Many laboratory devices are available to visualize illuminated living cells and these range from fluorescence microscopy to more advanced spectroscopy.

Key Terms

- **Spectroscopy**: use of light, sound or particle emission to study matter. The emissions provide information about the properties of the matter under investigation. The device often used for such analysis is a spectrometer, which records the spectrum of light emitted (or absorbed) by a given material.
- **Fluorescence microscopy**: optical microscope that uses fluorescence to study properties of substances. A sample is illuminated with light of a wavelength that excites fluorescence in the sample. The fluoresced light, which is usually at a longer wavelength than the illumination, is then imaged through a microscope objective.

Fluorescence and luminescence

Cells undergo many dynamic processes. In order to visualize these processes we need to be able to film cells over time. This can be achieved by using tools to monitor gene expression to track when proteins are made and where they go in the cell. In molecular biology, researchers use a reporter gene that they attach to a regulatory gene of interest. Reporter genes ideally have distinguishable properties that can be easily detected and measured. The most commonly used reporter genes have biofluorescent or bioluminescent characteristics and can be visualized with the aid of microscopy and other non-invasive imaging equipments. Examples of such reporters are the genes encoding for Green Fluorescent Protein (GFP) and luciferase, respectively. The discovery of GFP changed the way we look at cellular life today. GFP was first isolated from the jellyfish (*Aequorea victoria*) by the Japanese scientist Osuma Shimomura in the early 1960s. It was then cloned and its sequence identified in 1992 by Douglas Prasher. GFP is widely used in research laboratories as a marking tool to illuminate and track genes in fixed or living cells. Luciferase, isolated from fireflies, is an enzyme present in the cells of bioluminescent organisms that catalyzes the oxidation of luciferin and ATP producing light. Luciferase is similarly useful as a biological marker in living cells and organisms.

Transfection of reporter genes into cells

To introduce a reporter gene into an organism, scientists place the reporter gene and the gene of interest in the same DNA construct to be inserted into the cell or organism. For bacteria or prokaryotic cells in culture, this is usually in the form of a circular DNA molecule called a plasmid. It is important to use a reporter gene that is not natively expressed in the cell or organism under study, since the expression of the reporter is being used as a marker for successful uptake of the gene of interest. This gene's regulatory sequence now controls the production of GFP or luciferase, in addition to the protein of interest. In cells where the gene is expressed, and the tagged proteins are produced, GFP or luciferase are produced at the same time. Thus, only those cells in which the tagged gene is expressed, or the target proteins are produced, will fluoresce when observed under fluorescence microscopy, or bioluminesce (emit light) when luciferin, the substrate for luciferase is added.

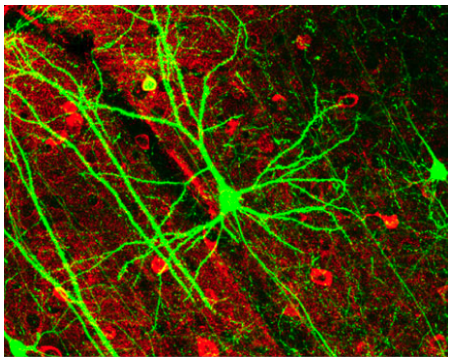

Figure: **Newly developed neurons in the hippocampus of the adult mouse**: Pyramidal neuron visualized by green fluorescent protein (GFP).

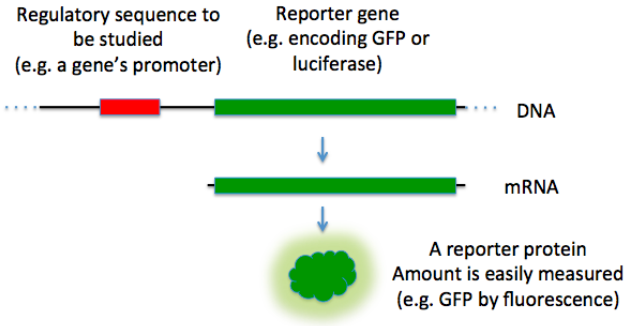

Figure: **Introducing a reporter gene into a cell**: Reporter gene used as an indication of the regulatory sequence expression in the cell.

Application of GFP in molecular microbiology

GFP has many advantages over conventional reporter genes in that it is highly stable, non-toxic to living cells and organisms, detection tools are non-invasive and the green light is generated without the addition of external cofactors and measured without application of expensive equipment. Various applications of that reporter gene were documented and vary from being able to monitor microorganism 's survival in complex biological systems such as activated sludge to biodegradation of chemical compounds in soil. GFP allowed the detection, determination of spatial location and enumeration of bacterial cells from diverse environmental samples such as biofilm and water. GFP as biomarker is also useful in monitoring gene expression and protein localisation in bacterial cells.

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7. 26C: Multiplex and Real-Time PCR

Multiplex and real-time PCR are molecular techniques designed to amplify nucleic acid sequences in a quantitative manner.

LEARNING OBJECTIVES

Illustrate the use and method of multiplex and real-time PCR

KEY TAKEAWAYS

Key Points

- Real-time PCR is a molecular tool for nucleic acid amplification monitored as the reaction progresses.
- Multiplex PCR technique can use fluorescence to detect, quantitate, and visualize PCR products on a computer monitor by utilizing numerous primer sets.
- Real-time PCR can be a simplex, amplifying one DNA template with one set of primers, or multiplex, amplifying one or more DNA templates with one or more sets of primers in one reaction.

Key Terms

- **agarose gel electrophoresis**: Method used for the separation of DNA fragments by size.
- **oligonucleotide**: A strand of nucleic acid that serves as a starting point for DNA synthesis.

Polymerase Chain Reaction (PCR) is a molecular technique commonly used to amplify nucleic acid sequences. The starting material is a messenger RNA (mRNA) of interest that could be obtained from a wide array of sample types and extracted using commercially available kits and reagents. This mRNA is used to synthesize complementary DNA (cDNA) in a reaction catalyzed by the enzyme reverse transcriptase. The importance of this step is it allows converting a labile RNA into its more stable cDNA form that can be stored and used for multiple applications. The resulting cDNA serves as the template for the PCR reaction. The PCR process can be divided into three steps: DNA denaturation where double-stranded DNA (dsDNA) is separated at temperatures above 90°C, oligonucleotide primers annealing at 50–60°C, and primer extension at 70–78°C. A programmable thermal cycler controls the rate of temperature change, the length of the incubation at each temperature, and the number of times each cycle of temperatures is repeated. The final product of the reaction is called amplicon. It is confirmed by agarose gel electrophoresis for qualitative results.



Figure: **Thermal Cycler**: Automated apparatus to amplify DNA sequences using the polymerase chain reaction.

Real-time polymerase chain (RT-PCR) reaction, also called quantitative real-time PCR (qRt-PCR) is used to amplify and quantify targeted DNA molecules. The use of RT-PCR allows for both detection and quantitation of DNA sequences. The quantity can be an absolute number of copies or a relative amount when normalized to DNA input or additional normalizing genes. The procedure for RT-PCR follows the general principles of PCR, but the defining feature is the ability to detect amplified DNA as the reaction progresses in real time.

Real-time PCR can used to amplify low-abundance DNA templates. It is useful in monitoring the accumulating amplicon. Two common methods that are used to product detection in real-time PCR include the use of non-specific flourescent dyes that intercalate with double-stranded DNA or sequence-specific DNA probes that consist of oligonucleotides labeled with a fluorescent reporter (oligoprobes). The fluorescent reporter permits detection after hybridization of the probe with its complementary DNA target. During real-time PCR with oligoprobes, there is a change in signal following direct interaction with the amplicon. The

signal is related to the amount of amplicon present during each cycle and will increase as the amount of specific amplicon increases. The detection of amplicon could be visualized on a graph as the amplification progresses. Real-time PCR assays have been extremely useful for studying microbial agents of infectious disease and have proven valuable for basic microbiological research. The ability to amplify templates from a broad selection of specimen has made it an ideal system for application across the various microbiological disciplines.

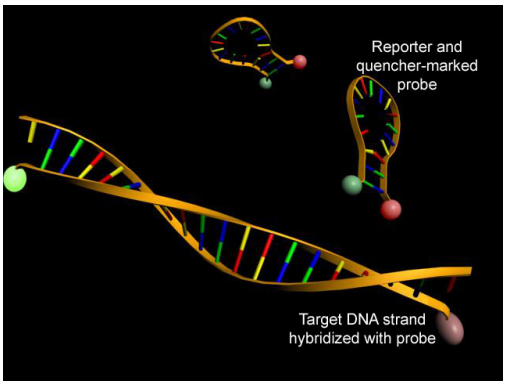

Figure: **Real-Time Polymerase Chain Reaction**: Real-Time PCR utilizes fluorescent probes to measure DNA amplification.

A new and improved technology called multiplex PCR was introduced to allow the use of one or more primer sets to potentially amplify multiple templates within a single reaction. Up to 20 different reactions can be run simultaneously, therefore lowering the amount of sample used, reducing the reagents consumed, and collecting far more information per reaction, while simplifying data analyses. Multiplex PCR is a challenging application that typically requires more optimization than standard, single amplicon PCR assays. The key to successful multiplex PCR is the ability to define a single set of reaction parameters (reagent concentrations and cycling parameters) that allows for all primers to anneal with high specificity to their target sequences and be extended with the same efficiency. Primer design, as well as the enzyme and buffer system, are critical factors in this challenge. The results from multiplex PCR can be analyzed using gel electrophoresis or using fluorophores for analysis using during the reaction. Ideally, a real-time multiplex PCR should be able to detect, differentiate, and provide a quantitative result for many different targets without a single target influencing the detection of one of the others (cross-talk) and without loss of sensitivity. It is evident that due to the limited number of fluorophoric labels available and the significant overlap in their emission spectra, quantification of multiplex reaction products is often difficult.

Numerous companies have helped overcome this issue by making dyes available that are compatible for use in multiplex PCR. Since its first description in 1988 by Chamberlain et al, this method has been applied in many areas of DNA testing, including analyses of deletions, mutations, and polymorphisms, or quantitative assays and reverse transcription PCR. Typically, it is used for genotyping applications where simultaneous analysis of multiple markers is required, detection of pathogens or genetically modified organisms, or for microsatellite analyses. Multiplex assays can be tedious and time-consuming to establish, requiring lengthy optimization procedures but once optimized numerous high-throughput genomic assays can be achieved at optimum speed.

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Thumbnail: A cladogram linking all major groups of living organisms to the LUCA (the black trunk at the bottom), based on ribosomal RNA sequence data.

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SECTION OVERVIEW

8.1: Origins of Life

Topic hierarchy

8.1A: Evidence of Evolution

8.1B: Elements of Life

8.1C: Unresolved Questions About the Origins of Life

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8.1A: Evidence of Evolution

Evidence for evolution has been obtained through fossil records, embryology, geography, and molecular biology.

LEARNING OBJECTIVES

Explain the development of the theory of evolution

KEY TAKEAWAYS

Key Points

- Fossils serve to highlight the differences and similarities between current and extinct species, showing the evolution of form over time.
- Similar anatomy across different species highlights their common origin and can be seen in homologous and vestigial structures.
- Embryology provides evidence for evolution since the embryonic forms of divergent groups are extremely similar.
- The natural distribution of species across different continents supports evolution; species that evolved before the breakup of the supercontinent are distributed worldwide, whereas species that evolved more recently are more localized.
- Molecular biology indicates that the molecular basis for life evolved very early and has been maintained with little variation across all life on the planet.

Key Terms

- **homologous structure**: the traits of organisms that result from sharing a common ancestor; such traits often have similar embryological origins and development
- **biogeography**: the study of the geographical distribution of living things
- **vestigial structure**: genetically determined structures or attributes that have apparently lost most or all of their ancestral function in a given species

Evidence of Evolution

The evidence for evolution is compelling and extensive. Looking at every level of organization in living systems, biologists see the signature of past and present evolution. Darwin dedicated a large portion of his book, *On the Origin of Species*, to identifying patterns in nature that were consistent with evolution. Since Darwin, our understanding has become clearer and broader.

Fossils, Anatomy, and Embryology

Fossils provide solid evidence that organisms from the past are not the same as those found today; they show a progression of evolution. Scientists calculate the age of fossils and categorize them to determine when the organisms lived relative to each other. The resulting fossil record tells the story of the past and shows the evolution of form over millions of years. For example, scientists have recovered highly-detailed records showing the evolution of humans and horses. The whale flipper shares a similar morphology to appendages of birds and mammals, indicating that these species share a common ancestor. Over time, evolution led to changes in the shapes and sizes of these bones in different species, but they have maintained the same overall layout. Scientists call these synonymous parts homologous structures.

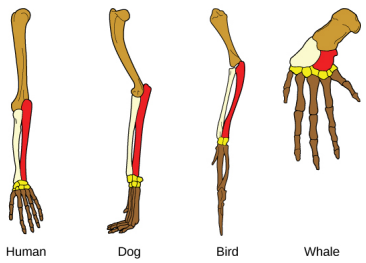

Figure: **Common Ancestors**: The similar construction of these appendages indicates that these organisms share a common ancestor.



(a) (b)

Figure: **Evolution of Humans and Horses**: (a) In this display, fossil hominids are arranged from oldest (bottom) to newest (top). As hominids evolved, the shape of the skull changed. (b) An artist's rendition of extinct species of the genus Equus reveals that these ancient species resembled the modern horse (Equus ferus), but varied in size.

Some structures exist in organisms that have no apparent function at all, appearing to be residual parts from a common ancestor. These unused structures (such as wings on flightless birds, leaves on some cacti, and hind leg bones in whales) are vestigial.

Embryology, the study of the development of the anatomy of an organism to its adult form, provides evidence for evolution as embryo formation in widely-divergent groups of organisms tends to be conserved. Structures that are absent in the adults of some groups often appear in their embryonic forms, disappearing by the time the adult or juvenile form is reached. For example, all vertebrate embryos, including humans, exhibit gill slits and tails at some point in their early development. These disappear in the adults of terrestrial groups, but are maintained in adults of aquatic groups, such as fish and some amphibians. Great ape embryos, including humans, have a tail structure during their development that is lost by birth.

Another form of evidence of evolution is the convergence of form in organisms that share similar environments. For example, species of unrelated animals, such as the arctic fox and ptarmigan living in the arctic region, have been selected for seasonal white phenotypes during winter to blend with the snow and ice. These similarities occur not because of common ancestry, but because of similar selection pressures: the benefits of not being seen by predators.



(a) (b)

Figure: **Adaptations: Winter Coats**: The white winter coat of the (a) arctic fox and the (b) ptarmigan's plumage are adaptations to their environments.

Biogeography

The geographic distribution of organisms on the planet follows patterns that are best explained by evolution in conjunction with the movement of tectonic plates over geological time. Broad groups that evolved before the breakup of the supercontinent Pangaea (about 200 million years ago) are distributed worldwide. Groups that evolved since the breakup appear uniquely in regions of the planet, such as the unique flora and fauna of northern continents that formed from the supercontinent Laurasia compared to that of the southern continents that formed from the supercontinent Gondwana.

The great diversification of marsupials in Australia and the absence of other mammals reflect Australia's long isolation. Australia has an abundance of endemic species (those found nowhere else) which is typical of islands whose isolation by expanses of water prevents species from migrating. Over time, these species diverge evolutionarily into new species that look very different from their ancestors that may exist on the mainland. The marsupials of Australia, the finches on the Galápagos, and many species on the Hawaiian Islands are all unique to their one point of origin, yet they display distant relationships to ancestral species on mainlands.

Like anatomical structures, the structures of the molecules of life reflect descent with modification. Evidence of a common ancestor for all of life is reflected in the universality of DNA as the genetic material, in the near universality of the genetic code, and in the machinery of DNA replication and expression. In general, the relatedness of groups of organisms is reflected in the similarity of their DNA sequences. This is exactly the pattern that would be expected from descent and diversification from a common ancestor.

DNA sequences have also shed light on some of the mechanisms of evolution. For example, it is clear that the evolution of new functions for proteins commonly occurs after gene duplications that allow the free modification of one copy by mutation, selection, or drift (changes in a population ‘s gene pool resulting from chance), while the second copy continues to produce a functional protein.

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8.1B: Elements of Life

Key elements were needed for early life to start on earth.

LEARNING OBJECTIVES

Define the key elements of life

KEY TAKEAWAYS

Key Points

- While the exact substituents for early life to form are not completely agreed upon, most theories agree that methane, ammonia, water, hydrogen sulfide, carbon dioxide or carbon monoxide, and phosphate were needed in the absence of molecular oxygen and ozone.
- From a soup of the primordial earth it's debated whether RNA or protein were the first molecules needed to start simple life, as both can catalyze their self-assembly.
- Once simple molecules formed on primordial earth they could then be placed under selective pressure to replicate, starting the evolution of the first life-forms on earth.

Key Terms

- **phospholipid**: any lipid like lecithin or cephalin consisting of a diglyceride combined with a phosphate group and a simple organic molecule likecholine or ethanolamine; they are important constituents of biological membranes
- **ribozyme**: A fragment of RNA that can act as an enzyme.

There is no "standard model" of the origin of life. However, most currently accepted models draw at least some elements from the framework laid out by the Oparin-Haldane hypothesis. The Oparin-Haldane hypothesis suggests that the atmosphere of the early Earth may have been chemically reducing in nature, composed primarily of: methane (CH_4), ammonia (NH_3), water (H_2O), hydrogen sulfide (H_2S), carbon dioxide (CO_2) or carbon monoxide (CO), with phosphate (PO_4^{3-}), molecular oxygen (O_2) and ozone (O_3) either rare or absent.

In such a reducing atmosphere, electrical activity can catalyze the creation of certain basic small molecules (monomers) of life, like amino acids. This was demonstrated in the Miller–Urey experiment by Stanley L. Miller and Harold C. Urey in 1953. Phospholipids (of an appropriate length) can form lipid bilayers, a basic component of the cell membrane.

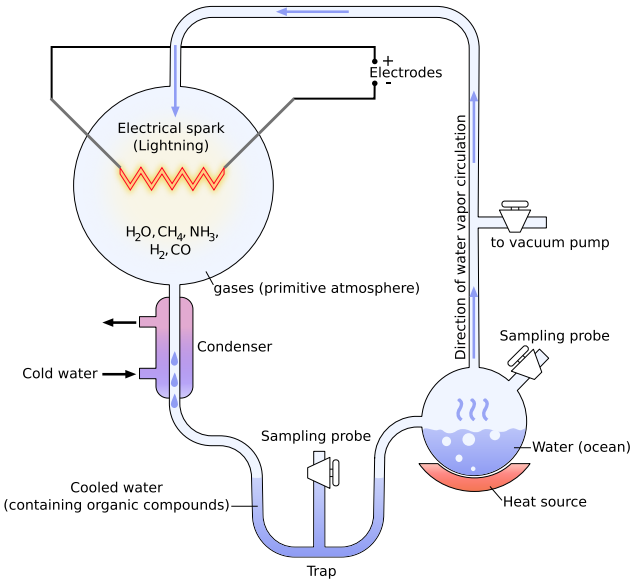

Figure: **Miler-Urey Experiment**: An outline of the apparatus used by Miller and Urey. Using this apparatus, and using conditions thought to approximate the conditions on pre-biotic earth, they were able to catalyze the molecules of life like amino acids.

A fundamental question is about the nature of the first self-replicating molecule. Since replication is accomplished in modern cells through the cooperative action of proteins and nucleic acids, the major schools of thought about how the process originated can be broadly classified as “proteins first” and “nucleic acids first. ” The principal thrust of the “nucleic acids first” argument is as follows:

1. The polymerization of nucleotides into random RNA molecules might have resulted in self-replicating ribozymes (RNA world hypothesis).
2. Selection pressures for catalytic efficiency and diversity might have resulted in ribozymes which catalyse peptidyl transfer (hence formation of small proteins), since oligopeptides complex with RNA to form better catalysts. The first ribosome might have been created by this process, resulting in more prevalent protein synthesis.
3. Synthesized proteins might then out-compete ribozymes in catalytic ability, therefore becoming the dominant biopolymer, relegating nucleic acids to their modern use as a carrier of genomic information.

Biologist John Desmond Bernal coined the term biopoiesis for this process,and suggested that there were a number of clearly defined “stages” that could be recognized in explaining the origin of life:

- Stage 1: The origin of biological monomers
- Stage 2: The origin of biological polymers
- Stage 3: The evolution from molecules to cell

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8.1C: Unresolved Questions About the Origins of Life

The question of how simple organic molecules formed a protocell is largely unanswered.

LEARNING OBJECTIVES

Outline key questions that are unknown about early life on earth

KEY TAKEAWAYS

Key Points

- Theoretical biologists can easily understand how a protocell can give rise to the life we see around us; however the question of how simple organic compounds can become the more complex constituents we see in life is more difficult to explain.
- Several problems exist with current abiogenesis models, including a primordial earth with conditions not inductive to abiogenesis, the lack of a method for simple organic molecules to polymerize, and the mono-chirality of molecules seen in life.
- A recent idea that the early earth was bombarded with complex organic molecules needed for life is gaining credence and may answer many criticisms that are apparent with terrestrial-based abiogenesis models.

Key Terms

- **protocell**: A self-organized, endogenously ordered, spherical collection of polypeptides proposed as a stepping-stone to the origin of life
- **enantiomer**: One of a pair of stereoisomers that is the mirror image of the other, but may not be superimposed on this other stereoisomer. Almost always, a pair of enantiomers contain at least one chiral center, and a sample of either enantiomer will be optically active.

There is substantial understanding of how inorganic molecules can give rise to somewhat simple building blocks of life in the process known as abiogenesis. For example, nucleic and amino acids can be made in laboratory simulations of the early earth, but how these acids polymerized to make the long chain needed for life is unknown. On the other hand, once a simple protocell capable of replication forms, upon encountering its specific antigen, evolution then takes it course and the myriad ways in which cells try to survive can be understood. However, the question of how simple organic molecules form a protocell is largely unanswered.

There are a few problems consistently seen in most scenarios of abiogenesis. One such problem involves polymerization. The thermodynamic equilibrium of amino acid versus peptides is in the direction of separate amino acids. However, a force that drives polymerization is missing. The random association of single amino acids into one short protein string of 100 amino acids without some enzymatic help could take an incredible amount of time, longer than the age of the earth. Several mechanisms for such polymerization have been suggested, but the resolution of this problem may well be in the properties of polyphosphates. Polyphosphates are formed by polymerization of ordinary monophosphate ions PO_4^{-3}. Polyphosphates cause polymerization of amino acids into peptides. They are also the logical precursors in the synthesis of key biochemical compounds such as ATP. A key issue seems to be that calcium reacts with soluble phosphate to form insoluble calcium phosphate (apatite), so some plausible mechanism must be found to keep calcium ions from causing precipitation of phosphate.

Further, experiments that show how simple organic molecules can form (like the Miller-Urey experiment) depend on the assumption that the early earth was a reducing environment, having little oxygen. However, current scientific consensus describes the primitive atmosphere as either a weakly-reducing or neutral. Such an atmosphere would diminish both the amount and variety of amino acids that could be produced.

One further problem confronting many abiogenesis models is homochirality. Homochirality is the term used to describe all building blocks in living organisms having the same “handedness” (amino acids being left-handed, nucleic acid sugars (ribose and deoxyribose) being right-handed, and chiral phosphoglycerides). Some process in chemical evolution must account for the origin of this phenomenon. Chiral molecules can be synthesized, but in the absence of a chiral source or a chiral catalyst, they are formed in a 50/50 mixture of both enantiomer.

There are many models that are being used to explain these problems and others; one that is quite intriguing is the idea that the early earth was actually bombarded by extraterrestrial organic molecules. It should be clear the term extraterrestrial in these abiogenesis models are not referring to little green men, but rather complex organic molecules, of which the abiogenesis occurred in the more favorable conditions for such reactions in space. For instance, the environment in space is strongly reducing (ie no

oxygen), and it has been suggested that meteorites introduced the phosphorus species to earth, which explains the need of monophosphate. Homochirality may also have started in space, as the studies of the amino acids on a meteorite showed L-alanine to be more than twice as frequent as its D form, and L-glutamic acid was more than 3 times prevalent than its D counterpart. While the idea of extraterrestrial abiogenesis once seemed far-fetched, the presence of organic molecules on meteorites (and recently in stars themselves) adds credence to this exciting possibility.

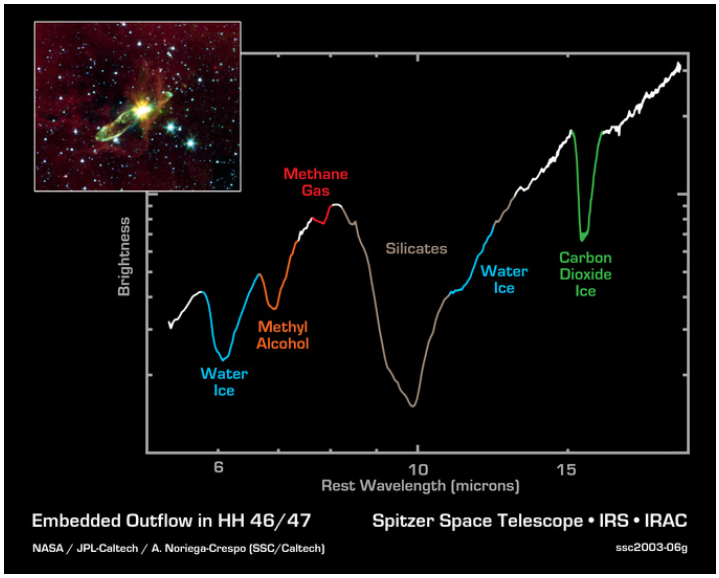

Figure: **Organic molecules detected in space**: NASA's Spitzer Space Telescope has lifted the cosmic veil to see an otherwise hidden newborn star, while detecting the presence of water and carbon dioxide ices, as well as organic molecules. The Spitzer image (inset) was obtained with the infrared array camera. The primary image shows a spectrum obtained with Spitzer's infrared spectrograph instrument, stretching from wavelengths of 5.5 microns to 20 microns. Spectra are graphical representations of a celestial object's unique blend of light. Characteristic patterns, or fingerprints, within the spectra allow astronomers to identify the object's chemical composition.

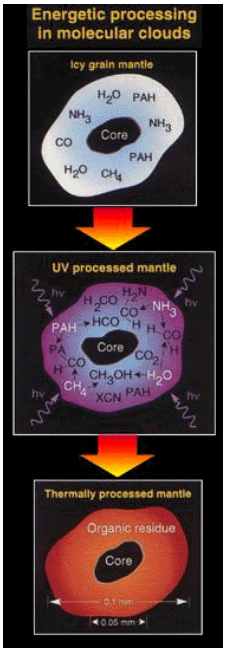

Figure: **Organic biogenesis**: A scheme depicting how organic molecules might be synthesized in space.

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SECTION OVERVIEW

8.2: Astrobiology

Astrobiology is the study of the origin, evolution, distribution, and future of life in the universe: extraterrestrial life and life on Earth.

Topic hierarchy

8.2A: Mars and a Biosphere

8.2B: Martian Biosignatures

8.2C: Terraforming Mars

8.2D: Europa's Possible Ocean

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8.2A: Mars and a Biosphere

Learning Objectives

- Discuss the Martian biosphere

Mars is the fourth planet from the Sun and the second smallest planet in the Solar System. The planet can be seen from Earth with the naked eye. Mars has a thin atmosphere and its surface is very similar to the Earth's moon (craters). Mars has volcanoes, valleys, deserts, and polar ice caps similar to Earth. Additionally, Mars rotates similarly to Earth and has a tilt that produces seasons.

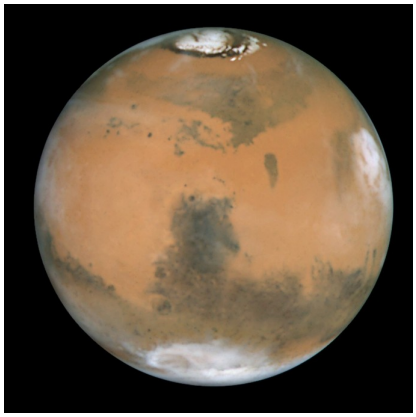

Figure: **Mars**: This is the true-color view of Mars as seen through NASA's Hubble Space Telescope in 1999.

Mars was first observed at close proximity in 1965 by the Mariner 4. This observation began decades of study and speculations about the structure of the surface of Mars. Scientists hypothesize that its surface is covered by liquid water. Scientists are still collecting and analyzing data concerning its surface. The planet is currently host to five functioning spacecraft: three in orbit—the Mars Odyssey, Mars Express, and Mars Reconnaissance Orbiter; and two on the surface—Mars Exploration Rover Opportunity and the Mars Science Laboratory Curiosity.

Biosphere

A biosphere is typically defined as the part of the Earth and its atmosphere capable of supporting life. A biosphere can also be thought of as an global ecological system that incorporates all living beings and their relationships with the lithosphere, hydrosphere, and atmosphere. Currently, a great deal of research is going into developing hypotheses on a Martian biosphere. This research overlaps greatly with Martian terraforming, which explores how humans might manipulate the Martian environment to make it stable for maintaining life. As mentioned above, scientists are still collecting a great deal of data on the structure and functioning of Mars. This is a burgeoning field of research.

Key Points

- Mars has a thin atmosphere and its surface is very similar to the Earth's moon (craters) and has volcanoes, valleys, deserts, and polar ice caps similar to Earth itself. Mars rotates similarly to Earth and has a tilt that produces seasons.
- Mars was first observed at close proximity in 1965 by the Mariner 4. Scientists hypothesize that the surface of Mars is covered by liquid water.
- Scientists are still collecting and analyzing data concerning the surface of Mars. The planet is currently host to five functioning spacecraft.
- A biosphere is an global ecological system that incorporates all living beings and their relationships with the lithosphere, hydrosphere, and atmosphere. A great deal of research is going into developing hypotheses on Martian biosphere. Results are currently inconclusive.

Key Terms

- **Solar System**: The Sun and all the heavenly bodies that orbit around it, including the eight planets, their moons, the asteroids, and comets.

- **Mars**: The fourth planet in the solar system. Symbol: 
- **planet**: A body which orbits the Sun directly and is massive enough to be in hydrostatic equilibrium (effectively meaning a spheroid) and to dominate its orbit. The eight planets in the Solar System are Mercury, Venus, Earth, Mars, Jupiter, Saturn, Uranus, and Neptune. Pluto was considered a planet until 2006 and has now been reclassified as a dwarf planet.

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8.2B: Martian Biosignatures

Learning Objectives

- Describe biosignatures

A biosignature is any substance – such as an element, isotope, molecule, or phenomenon – that provides scientific evidence of past or present life. It is important to understand that while the presence of these substances or events could be a result of past or present life, they are not definitive evidence and should not be treated as such. Scientists determine the significance of a biosignature not only by examining the probability of life creating it, but mostly by the improbability of abiotic processes producing it.

Martian Biosignatures

On Earth, normal mammalian functioning has produced a fog of chemicals that is not replicated by any chemical process. This fog is made up of large amounts of oxygen and small amounts of methane. This mixture of gases has also been observed in the atmosphere of the planet Mars. Due to scientific thought that this fog cannot be formed by a chemical process, logic concludes that there must be some source of life on the planet.

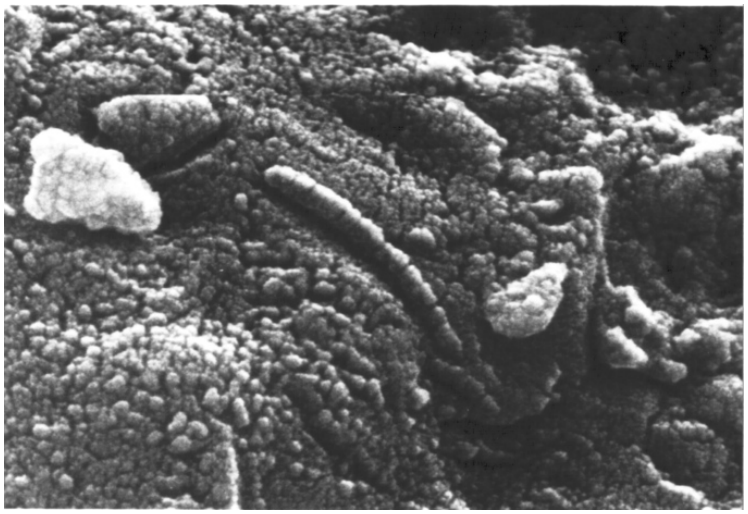

Figure: ***Martian Meteorite with Possible Fossilized Bacteria****: Some researchers suggest that these microscopic structures on the Martian meteorite could be fossilized bacteria.*

Scientists feel it is necessary to explore their hypotheses, so in the 1970s there were two American probes called Viking I and II that were sent to Mars to explore for life. The probes took images of the planet while in orbit and also while actually on the surface of Mars. The Viking landers carried three life-detection experiments that looked for signs of metabolism. Unfortunately, the imaging and life-detection results were inconclusive. There are plans for future missions to Mars, the Mars Science Laboratory and ExoMars, which will not only search for biosignatures but try to detect habitable environments as well.

Key Points

- A biosignature is any substance – such as an element, isotope, molecule, or phenomenon – that provides scientific evidence of past or present life.
- On Earth, normal mammalian functioning has produced a fog of chemicals that is not replicated by any chemical process. This mixture of gases has also been observed in the atmosphere of the planet Mars.
- In the 1970s there were two American probes called Viking I and II that were sent to Mars to explore the planet for life. The Viking landers carried three life-detection experiments that looked for signs of metabolism, but the imaging and life-detection results were inconclusive.
- There are plans for future missions to Mars to search for more evidence of biosignatures and habitable environments for life.

Key Terms

- **biosignature**: Any measurable phenomenon that indicates the presence of life.
- **metabolism**: The complete set of chemical reactions that occur in living cells.

- **abiotic**: Nonliving, inanimate, characterized by the absence of life; of inorganic matter.

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8.2C: Terraforming Mars

Terraforming Mars is the hypothetical idea that Mars could be altered in such a way to sustain human and terrestrial life forms.

LEARNING OBJECTIVES

Describe terraforming

KEY TAKEAWAYS

Key Points

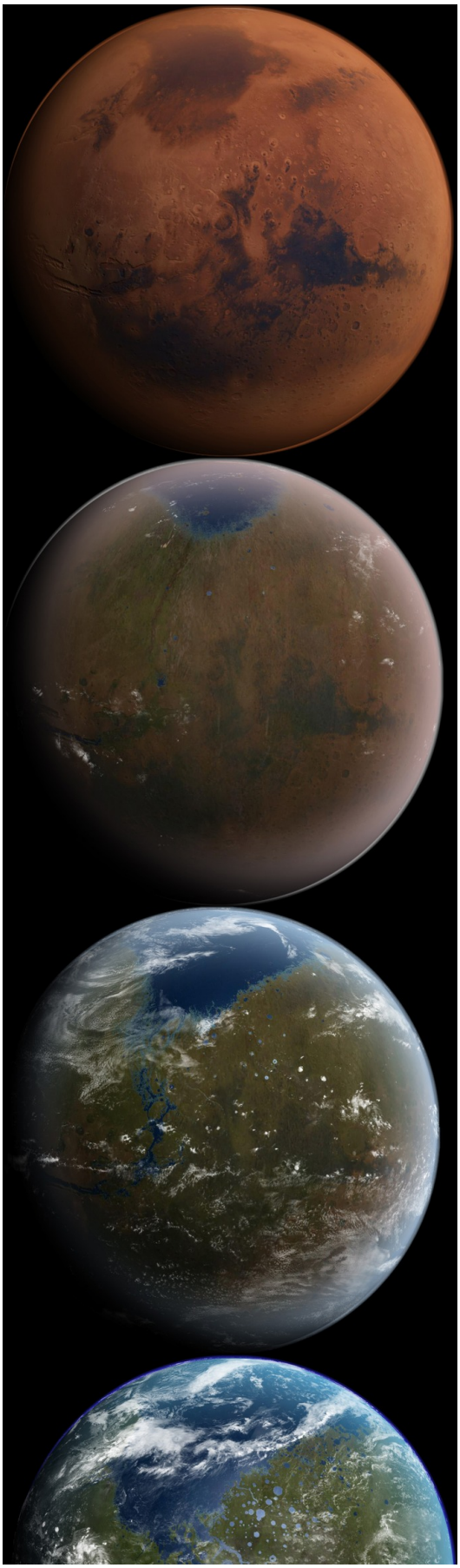
- The phrase “terraforming Mars ” refers to the idea that the planet Mars could be altered in such a way that it could sustain human and terrestrial life.
- The impact of terraforming Mars would be that in the face of global calamity, there would be a place outside of our planet that would be a safe haven for mankind.
- At this point, terraforming Mars is still a hypothetical idea.
- Scientists believe that water and oxygen are available on Mars in a form that could be easily manipulated to be usable by human and terrestrial life.
- Three major changes would have to occur for Mars to sustain life. These changes are: building up the pressure in the atmosphere, keeping it warm, and preventing the atmosphere from being lost to outer space.

Key Terms

- **Terraform**: To transform the atmosphere or biosphere of another planet into one having the characteristics of Earth.
- **electrolysis**: The chemical change produced by passing an electric current through a conducting solution or a molten salt.
- **Magnetosphere**: The comet-shaped region around Earth or another planet in which charged particles are trapped or deflected. It is shaped by the solar wind and the planet’s magnetic field.

Terraforming Mars

The phrase “terraforming Mars” refers to the idea that the planet Mars could be altered in a way so that it could sustain human and terrestrial life. For a deeper understanding of the term, “terra” literally means land or Earth, so mankind would essentially be making (or forming) this land to be more like Earth.



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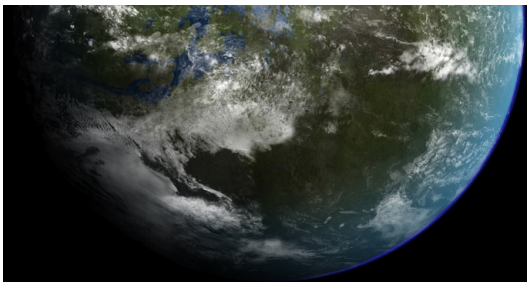

Figure: **Terraformed Mars**: This is an interpretation of what Mars might look like if it were terraformed.

Some people might question why exploring this hypothetical situation is important. The impact of terraforming Mars would be that in the face of global calamity, there would be a place outside of our planet that would be a safe haven for mankind. At this point, terraforming Mars is still a hypothetical idea.

The Process of Terraforming

For Mars to be suitable for human and terrestrial life, changes would be needed to be made to its climate, surface, and general properties. Although Mars is most like Earth out of all the planets in our solar system, it is still highly unsuitable for life as we know it. It is even thought that many years ago, Mars had a more suitable living environment with a thicker atmosphere and sufficient water to sustain life.

There are three major changes necessary for Mars to be suitable for life. The first change involves building up the atmosphere. This simply means that the surface pressure of Mars would need to be increased to sustain life. Currently, there is not a solution to this issue. Second, Mars would need to be kept warm. Scientists are focusing the least energy on solving this issue due to the amount of carbon dioxide on the planet. Carbon dioxide is a greenhouse gas which means that once the planet begins to heat, the excess carbon dioxide will probably help keep the heat near the ground. The last change that needs to be made is keeping the atmosphere from being lost to outer space. Solutions to this problem are not well-documented, but some scientists hypothesize that creating a magnetosphere would be helpful in resolving this issue.

It should be noted that water and oxygen supply are not listed in the necessary changes. Scientists have found that large amounts of water can be found below the Martian surface. It is currently mixed with dry ice (or frozen carbon dioxide), but it could be melted to be used as a water source. Additionally, it is hypothesized that through a process called electrolysis, scientists could separate the water molecules into oxygen and hydrogen to supply the planet with the necessary oxygen supply.

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8.2D: Europa's Possible Ocean

Learning Objectives

- Describe the evidence for oceans on Europa and the implications for life

Europa, discovered in 1610 by Galileo Galilei, is one of Jupiter's four moons (called the Galilean moons). Europa is covered by a layer of water/ice. It is fascinating to note that although Europa maintains a constant temperature of around -145 degrees Celsius, the water on its surface is not completely frozen (referred to as liquid water).



Figure: ***Europa****: An image of the Jovian moon Europa was acquired by Voyager 2*

Europa has tidal heating that develops from friction due to its eccentric orbit around Jupiter. In other words, in a similar fashion to the tides flowing in and out on Earth due to the moon's gravitational pull, the tides on Europa are affected due to its orbit around Jupiter and possibly also its orbital resonance with other Galilean moons. The planet 's gravitational pull is stronger on the near side than the far, creating tidal bulges that can crack the icy crust's surface and heat the interior. It has also been proposed that volcanoes deep under the moon's surface contain hydrothermal vents that heat and maintain the liquid water.

Scientists propose the Europa's smooth surface, with very few craters, must be the result of ice covering an ocean which evens out the surface. Originally there were hypotheses that the atmosphere burning up or weathering of the craters were the source of Europa's smooth surface, but these ideas were discarded due to Europa's thin atmosphere. Additionally, some parts of the moon's surface shows blocks of ice that are separated but seem to fit together like a puzzle. These icebergs could have been shifted by slushy or liquid water beneath. Ridges in Europa's landscape suggest existent water seeping up the ice cracks, refreezing, and then forming higher and higher ridges.

Geologists have analyzed images taken from the Voyager and Galileo expeditions and have come up with two possible models for the surface of this moon: the *thick-ice model* and the *thin-ice model*. The thick-ice model refers to Europa's large craters and their surrounding concentric rings. These rings are filled with what appears to be flat, fresh ice. Due to these observations and assumptions, combined with the calculated amount of heat present on the moon's surface, the outer crust of solid ice would be about 6-19 miles thick and the liquid water underneath would be about 60 miles deep. The thin-ice model, which is not widely supported by scientists, proposes that the icy crust would be only about 660 feet thick. Other scientists suggest that this layer is simply the outermost layer that changes constantly due to Europa's tides. Currently, there is little evidence to support this model.

Key Points

- Europa is covered by a layer of liquid ice even though it maintains a constant temperature of around -145 degrees Celsius.
- Europ, has tidal heating that develops from friction due to its eccentric orbit around Jupiter and its relationship with Jupiter's other moons (known as Galilean moons).
- It has also been proposed that volcanoes deep under the moon's surface contain hydrothermal vents that heat and maintain the liquid water.
- Scientists propose that Europa's smooth surface, with very few craters, must be the result of ice covering an ocean which evens out the surface.

- Geologists have analyzed images taken from the Voyager and Galileo expeditions and come up with two possible models for the surface of this moon, the thick-ice model and the thin-ice model. The thick-ice model is more widely held by scientists and has more evidence to support it.
- The thick-ice model notes Europa's craters and their surrounding concentric rings, which suggest the outer crust of ice would be about 6-19 miles thick and the liquid water underneath would be about 60 miles deep. The thin-ice model proposes that the icy crust would be about 660 ft thick.

Key Terms

- **Galileo**: Galileo was an unmanned NASA spacecraft which studied the planet Jupiter and its moons.
- **eccentric**: Not at or in the center; not perfectly circular.
- **Crater**: A hemispherical pit created by the impact of a meteorite or other object.

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SECTION OVERVIEW

8.3: Microbial Phylogeny

Topic hierarchy

8.3A: Processes and Patterns of Evolution

8.3B: Distinguishing between Similar Traits

8.3C: The Levels of Classification

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8.3A: Processes and Patterns of Evolution

Natural selection can only occur in the presence of genetic variation; environmental conditions determine which traits are selected.

Learning Objectives

- Explain why only heritable variation can be acted upon by natural selection

Key Points

- Genetic variation within a population is a result of mutations and sexual reproduction.
- A mutation may be neutral, reduce an organism's fitness, or increase an organism's fitness.
- An adaptation is a heritable trait that increases the survival and rate of reproduction of an organism in its present environment.
- Divergent evolution describes the process in which two species evolve in diverse directions from a common point.
- Convergent evolution is the process in which similar traits evolve independently in species that do not share a recent common ancestry.

Key Terms

- **adaptation**: modification of something or its parts that makes it more fit for existence under the conditions of its current environment
- **divergent evolution**: the process by which a species with similar traits become groups that are tremendously different from each other over many generations
- **convergent evolution**: a trait of evolution in which species not of similar recent origin acquire similar properties due to natural selection

Variation

Natural selection can only take place if there is variation, or differences, among individuals in a population. Importantly, these differences must have some genetic basis; otherwise, the selection will not lead to change in the next generation. This is critical because variation among individuals can be caused by non-genetic reasons, such as an individual being taller due to better nutrition rather than different genes.

Genetic diversity within a population comes from two main mechanisms: mutation and sexual reproduction. Mutation, a change in the DNA sequence, is the ultimate source of new alleles, or new genetic variation in any population. The genetic changes caused by mutation can have one of three outcomes:

- Many mutations will have no effect on the fitness of the phenotype; these are called neutral mutations.
- A mutation may affect the phenotype of the organism in a way that gives it reduced fitness (a lower likelihood of survival or fewer offspring).
- A mutation may produce a phenotype with a beneficial effect on fitness. Different mutations will have a range of effects on the fitness of an organism that expresses them in their phenotype, from a small effect to a great effect.

Sexual reproduction also leads to genetic diversity: when two parents reproduce, unique combinations of alleles assemble to produce the unique genotypes and thus phenotypes in each of the offspring. However, sexual reproduction can not lead to new genes, but rather provides a new combination of genes in a given individual.

Adaptations

A heritable trait that aids the survival and reproduction of an organism in its present environment is called an adaptation. Scientists describe groups of organisms becoming adapted to their environment when a change in the range of genetic variation occurs over time that increases or maintains the "fitness" of the population to its environment. The webbed feet of platypuses are an adaptation for swimming. The snow leopards' thick fur is an adaptation for living in the cold. The cheetahs' fast speed is an adaptation for catching prey.

Whether or not a trait is favorable depends on the environmental conditions at the time. The same traits are not always selected because environmental conditions can change. For example, consider a species of plant that grew in a moist climate and did not need to conserve water. Large leaves were selected because they allowed the plant to obtain more energy from the sun. Large leaves require more water to maintain than small leaves, and the moist environment provided favorable conditions to support large

leaves. After thousands of years, the climate changed and the area no longer had excess water. The direction of natural selection shifted so that plants with small leaves were selected because those populations were able to conserve water to survive the new environmental conditions.

The evolution of species has resulted in enormous variation in form and function. Sometimes, evolution gives rise to groups of organisms that become tremendously different from each other. When two species evolve in diverse directions from a common point, it is called divergent evolution. Such divergent evolution can be seen in the forms of the reproductive organs of flowering plants which share the same basic anatomies; however, they can look very different as a result of selection in different physical environments and adaptation to different kinds of pollinators.



Flowering Plants: Flowering plants evolved from a common ancestor. Notice that the (a) dense blazing star (Liatrus spicata) and the (b) purple coneflower (Echinacea purpurea) vary in appearance, yet both share a similar basic morphology.

In other cases, similar phenotypes evolve independently in distantly-related species. For example, flight has evolved in both bats and insects; they both have structures we refer to as wings, which are adaptations to flight. However, the wings of bats and insects have evolved from very different original structures. This phenomenon is called convergent evolution, where similar traits evolve independently in species that do not share a recent common ancestry. The two species came to the same function, flying, but did so separately from each other.

These physical changes occur over enormous spans of time and help explain how evolution occurs. Natural selection acts on individual organisms, which in turn can shape an entire species. Although natural selection may work in a single generation on an individual, it can take thousands or even millions of years for the genotype of an entire species to evolve. It is over these large time spans that life on earth has changed and continues to change.

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8.3B: Distinguishing between Similar Traits

Similar traits can be either homologous structures that share an embryonic origin or analogous structures that share a function.

Learning Objectives

- Explain the difference between homologous and analogous structures

Key Points

- Organisms may be very closely related, even though they look quite different, due to a minor genetic change that caused a major morphological difference.
- Unrelated organisms may appear very similar because both organisms developed common adaptations that evolved within similar environmental conditions.
- To determine the phylogeny of an organism, scientists must determine whether a similarity is homologous or analogous.
- The advancement of DNA technology, the area of molecular systematics, describes the use of information on the molecular level, including DNA analysis.

Key Terms

- **analogous**: when similar similar physical features occur in organisms because of environmental constraints and not due to a close evolutionary relationship
- **homologous**: when similar physical features and genomes stem from developmental similarities that are based on evolution
- **phylogeny**: the evolutionary history of an organism
- **molecular systematics**: molecular phylogenetics is the analysis of hereditary molecular differences, mainly in DNA sequences, to gain information on an organism's evolutionary relationships

Two Options for Similarities

In general, organisms that share similar physical features and genomes tend to be more closely related than those that do not. Such features that overlap both morphologically (in form) and genetically are referred to as homologous structures; they stem from developmental similarities that are based on evolution. For example, the bones in the wings of bats and birds have homologous structures.

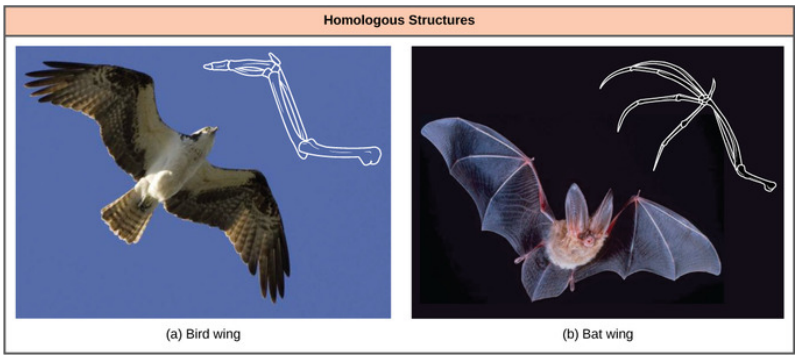

Figure: **Homologous structures**: Bat and bird wings are homologous structures, indicating that bats and birds share a common evolutionary past.

Notice it is not simply a single bone, but rather a grouping of several bones arranged in a similar way. The more complex the feature, the more probable that any overlap is due to a common evolutionary past. Imagine two people from different countries both inventing a car with all the same parts and in exactly the same arrangement without any previous or shared knowledge. That outcome would be highly improbable. However, if two people both invented a hammer, it would be reasonable to conclude that both could have the original idea without the help of the other. The same relationship between complexity and shared evolutionary history is true for homologous structures in organisms.

Misleading Appearances

Some organisms may be very closely related, even though a minor genetic change caused a major morphological difference to make them look quite different. Similarly, unrelated organisms may be distantly related, but appear very similar. This usually

happens because both organisms developed common adaptations that evolved within similar environmental conditions. When similar characteristics occur because of environmental constraints and not due to a close evolutionary relationship, it is called an analogy or homoplasy. For example, insects use wings to fly like bats and birds, but the wing structure and embryonic origin is completely different. These are called analogous structures.



Figure: **Analogous structures**: The (c) wing of a honeybee is similar in shape to a (b) bird wing and (a) bat wing, and it serves the same function. However, the honeybee wing is not composed of bones and has a distinctly-different structure and embryonic origin. These wing types (insect versus bat and bird) illustrate an analogy: similar structures that do not share an evolutionary history.

Similar traits can be either homologous or analogous. Homologous structures share a similar embryonic origin; analogous organs have a similar function. For example, the bones in the front flipper of a whale are homologous to the bones in the human arm. These structures are not analogous. The wings of a butterfly and the wings of a bird are analogous, but not homologous. Some structures are both analogous and homologous: the wings of a bird and the wings of a bat are both homologous and analogous. Scientists must determine which type of similarity a feature exhibits to decipher the phylogeny of the organisms being studied.

Molecular Comparisons

With the advancement of DNA technology, the area of molecular systematics, which describes the use of information on the molecular level including DNA analysis, has blossomed. New computer programs not only confirm many earlier classified organisms, but also uncover previously-made errors. As with physical characteristics, even the DNA sequence can be tricky to read in some cases. For some situations, two very closely-related organisms can appear unrelated if a mutation occurred that caused a shift in the genetic code. An insertion or deletion mutation would move each nucleotide base over one place, causing two similar codes to appear unrelated.

Sometimes two segments of DNA code in distantly-related organisms randomly share a high percentage of bases in the same locations, causing these organisms to appear closely related when they are not. For both of these situations, computer technologies have been developed to help identify the actual relationships. Ultimately, the coupled use of both morphologic and molecular information is more effective in determining phylogeny.

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8.3C: The Levels of Classification

Taxanomic classification divides species in a hierarchical system beginning with a domain and ending with a single species.

Learning Objectives

- Describe how taxonomic classification of organisms is accomplished and detail the levels of taxonomic classification from domain to species

Key Points

- Categories within taxonomic classification are arranged in increasing specificity.
- The most general category in taxonomic classification is domain, which is the point of origin for all species; all species belong to one of these domains: Bacteria, Archaea, and Eukarya.
- Within each of the three domains, we find kingdoms, the second category within taxonomic classification, followed by subsequent categories that include phylum, class, order, family, genus, and species.
- At each classification category, organisms become more similar because they are more closely related.
- As scientific technology advances, changes to the taxonomic classification of many species must be altered as inaccuracies in classifications are discovered and corrected.

Key Terms

- **binomial nomenclature**: the scientific system of naming each species of organism with a Latinized name in two parts
- **taxon**: any of the taxonomic categories such as phylum or subspecies
- **Linnaeus**: Swedish botanist, physician and zoologist who laid the foundations for the modern scheme of nomenclature; known as the “father of modern taxonomy”

The Levels of Classification

Taxonomy (which literally means “arrangement law”) is the science of classifying organisms to construct internationally-shared classification systems with each organism placed into more and more inclusive groupings. Think about how a grocery store is organized. One large space is divided into departments, such as produce, dairy, and meats. Then each department further divides into aisles, then each aisle into categories and brands, and then, finally, a single product. This organization from larger to smaller, more-specific categories is called a hierarchical system.

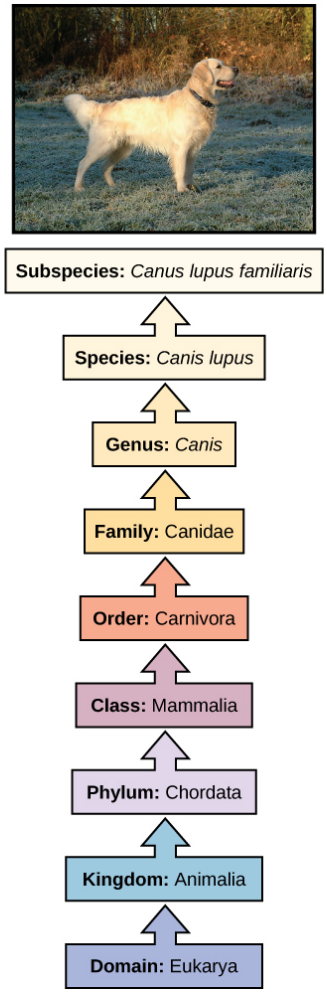

Figure: **Hierarchical models**: The taxonomic classification system uses a hierarchical model to organize living organisms into increasingly specific categories. The common dog, Canis lupus familiaris, is a subspecies of Canis lupus, which also includes the wolf and dingo.

The taxonomic classification system (also called the Linnaean system after its inventor, Carl Linnaeus, a Swedish botanist, zoologist, and physician) uses a hierarchical model. Moving from the point of origin, the groups become more specific, until one branch ends as a single species. For example, after the common beginning of all life, scientists divide organisms into three large categories called domains: Bacteria, Archaea, and Eukarya. Within each domain is a second category called a kingdom. After kingdoms, the subsequent categories of increasing specificity are: phylum, class, order, family, genus, and species.

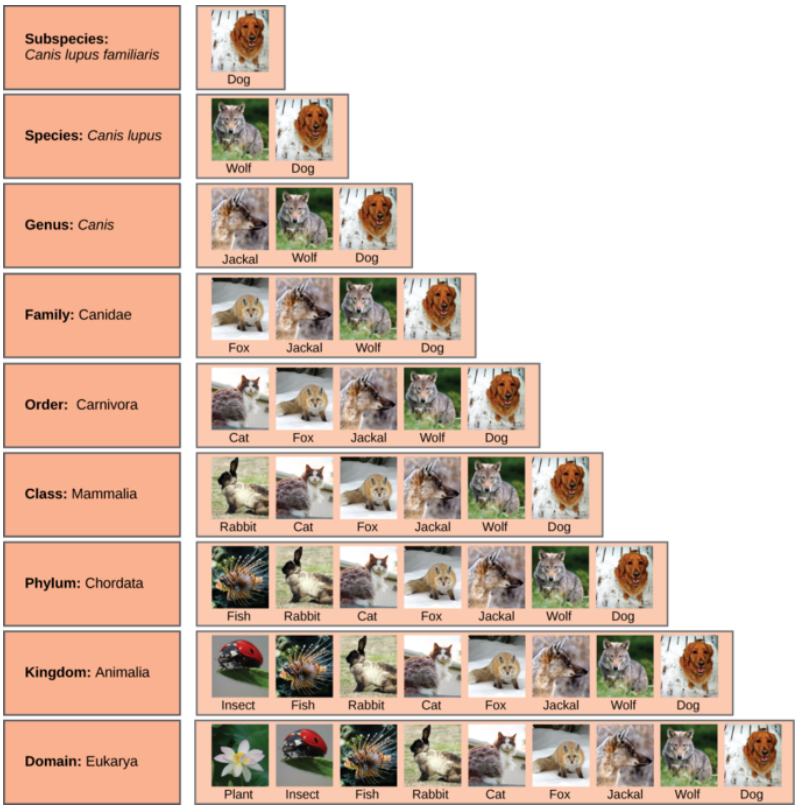

Figure: **Levels in taxonomic classification**: At each sublevel in the taxonomic classification system, organisms become more similar. Dogs and wolves are the same species because they can breed and produce viable offspring, but they are different enough to be classified as different subspecies.

The kingdom Animalia stems from the Eukarya domain. The full name of an organism technically has eight terms. For dogs, it is: Eukarya, Animalia, Chordata, Mammalia, Carnivora, Canidae, *Canis*, and *lupus*. Notice that each name is capitalized except for species and that genus and species names are italicized. Scientists generally refer to an organism only by its genus and species, which is its two-word scientific name, in what is called binomial nomenclature. Therefore, the scientific name of the dog is *Canis lupus*. The name at each level is also called a taxon. In other words, dogs are in order Carnivora. Carnivora is the name of the taxon at the order level; Canidae is the taxon at the family level, and so forth. Organisms also have a common name that people typically use; in this case, dog. Note that the dog is additionally a subspecies: the "familiaris" in *Canis lupus familiaris*. Subspecies are members of the same species that are capable of mating and reproducing viable offspring, but they are considered separate subspecies due to geographic or behavioral isolation or other factors.

Dogs actually share a domain (Eukarya) with the widest diversity of organisms, including plants and butterflies. At each sublevel, the organisms become more similar because they are more closely related. Historically, scientists classified organisms using physical characteristics, but as DNA technology developed, more precise phylogenies have been determined.

Recent genetic analysis and other advancements have found that some earlier phylogenetic classifications do not align with the evolutionary past; therefore, changes and updates must be made as new discoveries occur. Recall that phylogenetic trees are hypotheses and are modified as data becomes available. In addition, classification historically has focused on grouping organisms mainly by shared characteristics and does not necessarily illustrate how the various groups relate to each other from an evolutionary perspective. For example, despite the fact that a hippopotamus resembles a pig more than a whale, the hippopotamus may be the closest living relative to the whale.

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SECTION OVERVIEW

8.4: Classification of Microorganisms

Topic hierarchy

8.4A: The Taxonomic Scheme

8.4B: The Diagnostic Scheme

8.4C: The Species Concept in Microbiology

8.4D: Classification and Nomenclature

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8.4A: The Taxonomic Scheme

Bacterial taxonomy is the rank-based classification of bacteria.

Learning Objectives

- Outline the factors that play a role in the classification of bacterial taxonomy

Key Points

- Bacterial species differ amongst each other based on several characteristics, allowing for their identification and classification.
- Gram staining results are most commonly used as a classification tool.
- In 1987 Carl Woese divided the Eubacteria into 11 divisions based on 16S ribosomal RNA (SSU) sequences, which with several additions are still used today.

Key Terms

- **bacteria**: A type, species, or strain of bacterium.
- **taxonomy**: the academic discipline of defining groups of biological organisms on the basis of shared characteristics and giving names to those groups. Each group is given a rank and groups of a given rank can be aggregated to form a super group of higher rank and thus create a hierarchical classification.
- **Gram stain**: Gram staining (or Gram's method) is a method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative).It is based on the chemical and physical properties of their cell walls. Primarily, it detects peptidoglycan, which is present in a thick layer in Gram positive bacteria. A Gram positive results in a purple/blue color while a Gram negative results in a pink/red color.

Taxonomic Systems

Bacterial taxonomy is the rank-based classification of bacteria. In the scientific classification established by Carl von Linné, each distinct species is assigned to a genus using a two-part binary name (for example, *Homo sapiens).* This distinct species is then in turn placed within a lower level of a hierarchy of ranks. These ranks range in ascending scale from family to suborder, and upward to order, subclass, class, division/phyla, kingdom and domain.

In the currently accepted scientific classification of Life, there are three domains of microorganisms: the Eukaryotes, Bacteria and Archaea, The different disciplines of study refer to them using differing terms to speak of aspects of these domains, however, though they follow similar principles. Thus botany, zoology, mycology, and microbiology use several different conventions when discussing these domains and their subdivisions. In zoology, for example, there are *type specimens*, whereas in microbiology there are *type strains*.

Historical Challenges of Classification

Despite there being little agreement on the major subgroups of the Bacteria, gram staining results were commonly used as a classification tool. As an example, Prokaryotes share many common features, such as lack of nuclear membrane, unicellularity, division by binary-fission and generally small size. Until the advent of molecular phylogeny the Kingdom Prokaryotae was divided into four divisions, a classification scheme still formally followed by Bergey's manual of systematic bacteriology.The various species differ amongst each other based on several characteristics determined by gram staining, which allowed their identification and classification. Major groups of this system include: Gracilicutes (gram negative); Firmacutes (gram positive); Mollicutes (gram variable, e.g. Mycoplasma); and Mendocutes (uneven gram stain, "metlynogenic bacteria" now known as the Archaea).

Molecular Classification

In the Molecular era of classification, Carl Woese, who is regarded as the forerunner of the molecular phylogeny revolution, argued that the bacteria, archaea, and eukaryotes represent separate lines of descent that diverged early on from an ancestral colony of organisms. However, a few biologists argue that the Archaea and Eukaryota arose from a group of bacteria. In any case, it is thought that viruses and archaea began relationships approximately two billion years ago, and that co-evolution may have been occurring between members of these groups. It is possible that the last common ancestor of the bacteria and archaea was a thermophile, which raises the possibility that lower temperatures are "extreme environments" in archaeal terms, and organisms that

live in cooler environments appeared only later. Since the Archaea and Bacteria are no more related to each other than they are to eukaryotes, the term prokaryote's only surviving meaning is "not a eukaryote", limiting its value.

With improved methodologies it became clear that the methanogenic bacteria were profoundly different and were erroneously believed to be relics of ancient bacteria. Thus, though Woese identified three primary lines of descent the Archaebacteria, the Eubacteria and the Urkaryotes, the latter now represented by the nucleocytoplasmic component of the Eukaryotes. these lineages were formalised into the rank Domain (regio in Latin) which divided Life into 3 domains: the Eukaryota, the Archaea and the Bacteria. This scheme is still followed today.

In 1987 Carl Woese divided the Eubacteria into 11 divisions based on 16S ribosomal RNA (SSU) sequences, which with several additions are still used today.

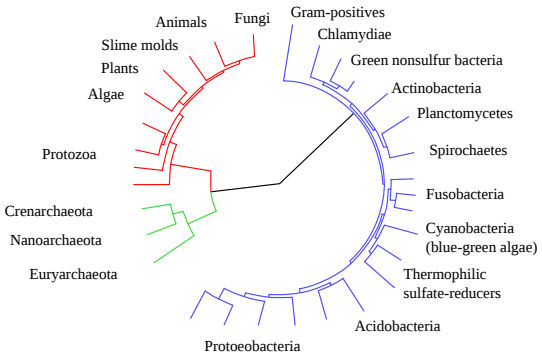

Figure: **Prokaryote phylogeny diagram**: Phylogenetic tree showing the relationship between the archaea and other forms of life. Eukaryotes are colored red, archaea green and bacteria blue.

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8.4B: The Diagnostic Scheme

Diagnosis of infectious disease sometimes involves identifying an infectious agent either directly or indirectly.

Learning Objectives

- Outline the various types of diagnostic methods used to diagnose a microbial infection

Key Points

- Diagnosis of infectious disease is nearly always initiated by medical history and physical examination.
- Culture allows identification of infectious organisms by examining their microscopic features, by detecting the presence of substances produced by pathogens, and by directly identifying an organism by its genotype.
- Diagnostic methods include: Microbial culture, microscopy, biochemical tests and molecular diagnostics.

Key Terms

- **Diagnosis**: Diagnosis of infectious disease sometimes involves identifying an infectious agent either directly or indirectly. In practice most minor infectious diseases such as warts, cutaneous abscesses, respiratory system infections and diarrheal diseases are diagnosed by their clinical presentation.
- **infectious**: Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.

The Challenge of Diagnosis

Diagnosis of infectious disease sometimes involves identifying an infectious agent either directly or indirectly. In practice most minor infectious diseases such as warts, cutaneous abscesses, respiratory system infections and diarrheal diseases are diagnosed by their clinical presentation. Conclusions about the cause of the disease are based upon the likelihood that a patient came in contact with a particular agent, the presence of a microbe in a community, and other epidemiological considerations. Given sufficient effort, all known infectious agents can be specifically identified. The benefits of identification, however, are often greatly outweighed by the cost, as often there is no specific treatment, the cause is obvious, or the outcome of an infection is benign.

Primary and Opportunistic Pathogens

Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. The appearance and severity of disease resulting from any pathogen depends upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen. Clinicians therefore classify infectious microorganisms or microbes according to the status of host defenses – either as primary pathogens or as opportunistic pathogens.

An Orderly Process

Diagnosis of infectious disease is nearly always initiated by taking a medical history and performing a physical examination. More detailed identification techniques involve the culture of infectious agents isolated from a patient. Culture allows identification of infectious organisms by examining their microscopic features, by detecting the presence of substances produced by pathogens, and by directly identifying an organism by its genotype. Other techniques, such as X-rays, CAT scans, PET scans or NMR, are used to produce images of internal abnormalities resulting from the growth of an infectious agent. The images are useful in detection of, for example, a bone abscess or a spongiform encephalopathy produced by a prion.

Diagnostic methods include microbial culture, microscopy, biochemical tests and molecular diagnostics:

- Microbiological culture is a principal tool used to diagnose infectious disease. In a microbial culture, a growth medium is provided for a specific agent. A sample taken from potentially diseased tissue or fluid is then tested for the presence of an infectious agent able to grow within that medium.

- Microscopy may be carried out with simple instruments, such as the compound light microscope, or with instruments as complex as an electron microscope. Samples obtained from patients may be viewed directly under the light microscope, and can often rapidly lead to identification. Microscopy is often also used in conjunction with biochemical staining techniques, and can be made exquisitely specific when used in combination with antibody based techniques.
- Biochemical tests used in the identification of infectious agents include the detection of metabolic or enzymatic products characteristic of a particular infectious agent. Since bacteria ferment carbohydrates in patterns characteristic of their genus and species, the detection of fermentation products is commonly used in bacterial identification. Acids, alcohols and gases are usually detected in these tests when bacteria are grown in selective liquid or solid media.
- Molecular diagnostics using technologies based upon the polymerase chain reaction (PCR) method will become nearly ubiquitous gold standards of diagnostics of the near future, for several reasons. First, the catalog of infectious agents has grown to the point that virtually all of the significant infectious agents of the human population have been identified. Second, an infectious agent must grow within the human body to cause disease; essentially it must amplify its own nucleic acids in order to cause a disease. This amplification of nucleic acid in infected tissue offers an opportunity to detect the infectious agent by using PCR. Third, the essential tools for directing PCR, primers, are derived from the genomes of infectious agents, and with time those genomes will be known, if they are not already.

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8.4C: The Species Concept in Microbiology

The number of species of bacteria and archaea is surprisingly small, despite their early evolution, genetic, and ecological diversity.

Learning Objectives

- Describe the concept of polyphasic species

Key Points

- The differences in species concepts between the Bacteria and macro-organisms, the difficulties in growing/characterising in pure culture (a prerequisite to naming new species, *vide supra*), and extensive horizontal gene transfer blurring the distinction of species makes differentiation difficult.
- The most commonly accepted definition is the *polyphasic species* definition, which takes into account both phenotypic and genetic differences.
- A quicker diagnostic threshhold is to separate species as less than 70% DNA -DNA hybridization, which corresponds to less than 97% 16S DNA sequence identity.

Key Terms

- **bacteria**: Bacteria constitute a large domain of prokaryotic microorganisms. Typically a few micrometres in length, bacteria have a wide range of shapes, ranging from spheres to rods and spirals. Bacteria were among the first life forms to appear on Earth, and are present in most habitats on the planet.
- **species**: In biology, a species is one of the basic units of biological classification and a taxonomic rank. A species is often defined as a group of organisms capable of interbreeding and producing fertile offspring.
- **DNA hybridization**: Hybridization is the process of establishing a non-covalent, sequence-specific interaction between two or more complementary strands of nucleic acids into a single complex, which in the case of two strands is referred to as a duplex. Oligonucleotides, DNA, or RNA will bind to their complement under normal conditions, so two perfectly complementary strands will bind to each other readily.

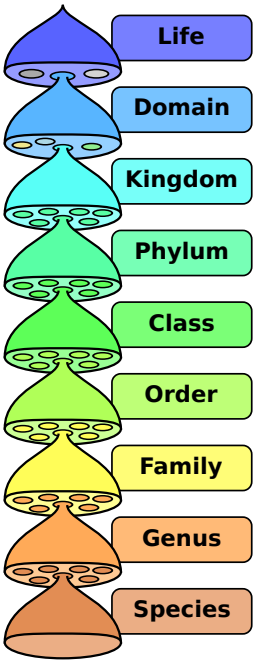

Figure: **Biological classification**: The hierarchy of biological classification's eight major taxonomic ranks. A genus contains one or more species. Intermediate minor rankings are not shown.

Judging Species in an Asexual Context

Bacteria divide asexually and for the most part do not show regionalisms. In other words, "Everything is everywhere. " Accordingly, the concept of species which works best for animals, becomes entirely a matter of judgement.

The approximately 5000 species of bacteria and archaea constitute a surprisingly small number, considering their relatively early evolution, genetic diversity, and ability to reside in all ecosystems on Earth. The reason for this numerical peculiarity lies in the differences in species concepts between the bacteria and macro-organisms and in the difficulties in growing and characterizing in pure culture (a prerequisite to naming new species, *vide supra*). In addition, the extensive amount of horizontal gene transfer among microorganisms results in the blurring of the distinctions between species among microorganisms.

The most commonly accepted definition is the *polyphasic species* definition,which takes into account both phenotypic and genetic differences. However, a quicker diagnostic ad hoc threshhold to separate species is less than 70% DNA-DNA hybridization, which corresponds to less than 97% 16S DNA sequence identity. It has been noted that if this were applied to animal classification the order of Primates would be considered a single species.

The International Journal of Systematic Bacteriology/International Journal of Systematic and Evolutionary Microbiology (IJSB/IJSEM) is a peer-reviewed journal that acts as the official international forum for the publication of new prokaryotic taxa. If a species is published in a different peer review journal, the author can submit a request to IJSEM with the appropriate description. If the information is correct, the new species will be featured in the Validation List of IJSEM.

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8.4D: Classification and Nomenclature

Nomenclature is the set of rules and conventions that govern the names of taxa.

Learning Objectives

- Recognize the factors involved with general classification and nomenclature used for microorganism classification

Key Points

- The names (nomenclature) given to prokaryotes are regulated by the International Code of Nomenclature of Bacteria (Bacteriological Code).
- Classification is the grouping of organisms into progressively more inclusive groups based on phylogeny and phenotype, while nomenclature is the application of formal rules for naming organisms.
- Taxonomic names are written in italics (or underlined when handwritten) with a majuscule first letter, with the exception of epithets for species and subspecies.

Key Terms

- **nomenclature**: binomial nomenclature (also called binominal nomenclature or binary nomenclature) is a formal system of naming species of living things by giving each a name composed of two parts, both of which use Latin grammatical forms, although they can be based on words from other languages. Such a name is called a binomial name (which may be shortened to just “binomial”), a binomen or a scientific name; more informally it is also called a Latin name.
- **prokaryotes**: (/proʊkæri.oʊts/, pro-kah-ree-otes or /proʊkæriəts/, pro-kah-ree-əts) a group of organisms whose cells lack a cell nucleus (karyon), or any other membrane-bound organelles. Most prokaryotes are unicellular organisms, although a few such as myxobacteria have multicellular stages in their life cycles.
- **Bacteriological code**: The International Code of Nomenclature of Bacteria (ICNB) or Bacteriological Code (BC) governs the scientific names for bacteria, including Archaea. It denotes the rules for naming taxa of bacteria, according to their relative rank. As such it is one of the Nomenclature Codes of biology.

Nomenclature is the set of rules and conventions which govern the names of taxa. It is the application of formal rules for naming organisms. Classification is the grouping of organisms into progressively more inclusive groups based on phylogeny and phenotype. Despite there being no official and complete classification of prokaryotes, the names (nomenclature) given to prokaryotes are regulated by the International Code of Nomenclature of Bacteria (Bacteriological Code), a book which contains general considerations, principles, rules, and various notes and advises in a similar fashion to the nomenclature codes of other groups.



Figure: **International Journal of Systematic and Evolutionary Microbiology (IJSEM)**: The IJSEM covers the naming of new bacteria and how they fit evolutionarily.

The taxa which have been correctly described are reviewed in Bergey’s manual of Systematic Bacteriology, which aims to aid in the identification of species and is considered the highest authority. An online version of the taxonomic outline of bacteria and archaea is available. Taxonomic names are written in italics (or underlined when handwritten) with a majuscule first letter with the exception of epithets for species and subspecies. Despite it being common in zoology, tautonyms (e.g. Bison bison) are not acceptable and names of taxa used in zoology, botany or mycology cannot be reused for bacteria (Botany and Zoology do share names).

For bacteria, valid names must have a Latin or Neolatin name and can only use basic latin letters (w and j inclusive, see History of the Latin alphabet for these), consequently hyphens, accents and other letters are not accepted and should be translitterated

correctly (e.g. ß=ss). Ancient Greek being written in the Greek alphabet, needs to be translitterated into the Latin alphabet.

Many species are named after people, either the discoverer or a famous person in the field of microbiology, for example Salmonella is after D.E. Salmon, who discovered it (albeit as “Bacillus typhi”). For the generic epithet, all names derived from people must be in the female nominative case, either by changing the ending to -a or to the diminutive -ella, depending on the name. For the specific epithet, the names can be converted into either adjectival form (adding -nus (m.), -na (f.), -num (n.) according to the gender of the genus name) or the genitive of the latinised name.

Many species (the specific epithet) are named after the place they are present or found (e.g. Borrelia burgdorferi). Their names are created by forming an adjective by joining the locality’s name with the ending -ensis (m. or f.) or ense (n.) in agreement with the gender of the genus name, unless a classical Latin adjective exists for the place. However, names of places should not be used as nouns in the genitive case.

For the Prokaryotes (Bacteria and Archaea) the rank kingdom is not used (although some authors refer to phyla as kingdoms). If a new or amended species is placed in new ranks, according to Rule 9 of the Bacteriological Code the name is formed by the addition of an appropriate suffix to the stem of the name of the type genus. For subclass and class the reccomendation from is generally followed, resulting in a neutral plural, however a few names do not follow this and instead keep into account Graeco-Latin grammar (e.g. the female plurals Thermotogae, Aquificae, and Chlamydiae, the male plurals Chloroflexi, Bacilli, and Deinococci, and the Greek plurals Spirochaetes, Gemmatimonadetes, and Chrysiogenetes).

Phyla are not covered by the Bacteriological Code, however, the scientific community generally follows the Ncbi and Lpsn taxonomy, where the name of the phylum is generally the plural of the type genus, with the exception of the Firmicutes, Cyanobacteria, and Proteobacteria, whose names do not stem from a genus name. The higher taxa proposed by Cavalier-Smith are generally disregarded by the molecular phylogeny community (vide supra).

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SECTION OVERVIEW

8.5: Methods of Classifying and Identifying Microorganisms

Topic hierarchy

8.5A: Phenotypic Analysis

8.5B: Classification of Prokaryotes

8.5C: Phylogenetic Analysis

8.5D: Nongenetic Categories for Medicine and Ecology

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8.5A: Phenotypic Analysis

Microorganisms can be classified on the basis of cell structure, cellular metabolism, or on differences in cell components.

Learning Objectives

- Distinguish between phenotypic characteristics for Bacteria, Archaea and Eukaryotes

Key Points

- The relationship between the three domains (Bacteria, Archaea, and Eukaryota) is of central importance for understanding the origin of life. Most of the metabolic pathways are common between Archaea and Bacteria, while most genes involved in genome expression are common between Archaea and Eukarya.
- Microorganisms are very diverse. They include bacteria, fungi, algae, and protozoa; microscopic plants, and animals. Single-celled microorganisms were the first forms of life to develop on earth, approximately 3 billion–4 billion years ago.
- The Gram stain characterizes bacteria based on the structural characteristics of their cell walls. By combining morphology and Gram-staining, most bacteria can be classified as belonging to one of 4 groups (Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci, and Gram-negative bacilli).
- There are some basic differences between Bacteria, Archaea, and Eukaryotes in cell morphology and structure which aid in phenotypic classification and identification.

Key Terms

- **Gram stain**: A method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative).
- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **domain**: In the three-domain system, one of three taxa at that rank: Bacteria, Archaea, or Eukaryota.

Microorganisms are very diverse. They include bacteria, fungi, algae, and protozoa; microscopic plants (green algae); and animals such as rotifers and planarians. Most microorganisms are unicellular (single-celled), but this is not universal.

Single-celled microorganisms were the first forms of life to develop on earth, approximately 3 billion–4 billion years ago. Further evolution was slow, and for about 3 billion years in the Precambrian eon, all organisms were microscopic. So, for most of the history of life on earth the only forms of life were microorganisms. Bacteria, algae, and fungi have been identified in amber that is 220 million years old, which shows that the morphology of microorganisms has changed little since the Triassic period. When at the end of the 19thcentury information began to accumulate about the diversity within the bacterial world, scientists started to include the bacteria in phylogenetic schemes to explain how life on earth may have developed. Some of the early phylogenetic trees of the prokaryote world were morphology-based. Others were based on the then-current ideas on the presumed conditions on our planet at the time that life first developed.

Microorganisms tend to have a relatively rapid evolution. Most microorganisms can reproduce rapidly, and microbes such as bacteria can also freely exchange genes through conjugation, transformation, and transduction, even between widely-divergent species. This horizontal gene transfer, coupled with a high mutation rate and many other means of genetic variation, allows microorganisms to swiftly evolve (via natural selection) to survive in new environments and respond to environmental stresses.

The relationship between the three domains (Bacteria, Archaea, and Eukaryota) is of central importance for understanding the origin of life. Most of the metabolic pathways, which comprise the majority of an organism's genes, are common between Archaea and Bacteria, while most genes involved in genome expression are common between Archaea and Eukarya. Within prokaryotes, archaeal cell structure is most similar to that of Gram-positive bacteria.

Phenotypic Methods of Classifying and Identifying Microorganisms

Classification seeks to describe the diversity of bacterial species by naming and grouping organisms based on similarities. Microorganisms can be classified on the basis of cell structure, cellular metabolism, or on differences in cell components such as DNA, fatty acids, pigments, antigens, and quinones.

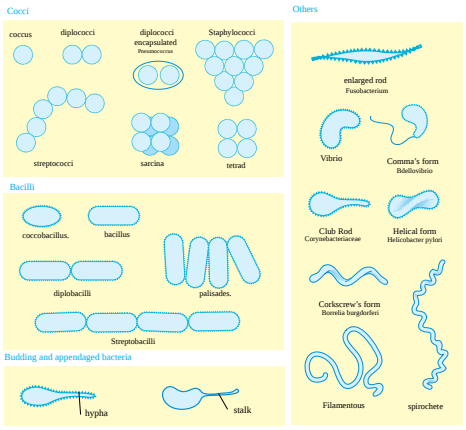

Figure: **Bacterial Morphology**: Basic morphological differences between bacteria. The most often found forms and their associations.

There are some basic differences between Bacteria, Archaea, and Eukaryotes in cell morphology and structure which aid in phenotypic classification and identification:

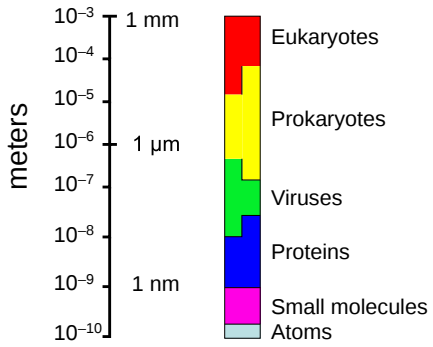

Figure: **The relative sizes of prokaryotic cells**: Relative scales of eukaryotes, prokaryotes, viruses, proteins and atoms (logarithmic scale).

- Bacteria: lack membrane -bound organelles and can function and reproduce as individual cells, but often aggregate in multicellular colonies. Their genome is usually a single loop of DNA, although they can also harbor small pieces of DNA called plasmids. These plasmids can be transferred between cells through bacterial conjugation. Bacteria are surrounded by a cell wall, which provides strength and rigidity to their cells.
- Archaea: In the past, the differences between bacteria and archaea were not recognized and archaea were classified with bacteria as part of the kingdom Monera. Archaea are also single-celled organisms that lack nuclei. Archaea in fact differ from bacteria in both their genetics and biochemistry. While bacterial cell membranes are made from phosphoglycerides with ester bonds, archaean membranes are made of ether lipids.
- Eukaryotes: Unlike bacteria and archaea, eukaryotes contain organelles such as the cell nucleus, the Golgi apparatus, and mitochondria in their cells. Like bacteria, plant cells have cell walls and contain organelles such as chloroplasts in addition to the organelles in other eukaryotes.

The Gram stain, developed in 1884 by Hans Christian Gram, characterizes bacteria based on the structural characteristics of their cell walls. The thick layers of peptidoglycan in the “Gram-positive” cell wall stain purple, while the thin “Gram-negative” cell wall appears pink. By combining morphology and Gram-staining, most bacteria can be classified as belonging to one of four groups (Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci, and Gram-negative bacilli). Some organisms are best identified by stains other than the Gram stain, particularly mycobacteria or Nocardia, which show acid-fastness on Ziehl–Neelsen or similar stains. Other organisms may need to be identified by their growth in special media, or by other techniques, such as serology.

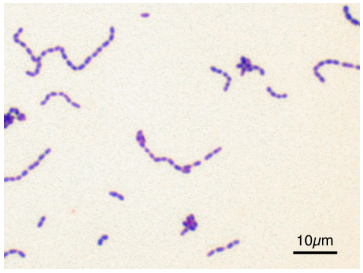

Figure: **Gram-positive bacteria**: Streptococcus mutans visualized with a Gram stain.

While these schemes allowed the identification and classification of bacterial strains, it was unclear whether these differences represented variation between distinct species or between strains of the same species. This uncertainty was due to the lack of distinct structures in most bacteria, as well as lateral gene transfer between unrelated species. Due to lateral gene transfer, some closely related bacteria can have very different morphologies and metabolisms. To overcome this uncertainty, modern bacterial classification emphasizes molecular systematics, using genetic techniques such as guanine cytosine ratio determination, genome-genome hybridization, as well as sequencing genes that have not undergone extensive lateral gene transfer, such as the rRNA gene.

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8.5B: Classification of Prokaryotes

Prokaryotic organisms were the first living things on earth and still inhabit every environment, no matter how extreme.

Learning Objectives

- Discuss the origins of prokaryotic organisms in terms of the geologic timeline

Key Points

- All living things can be classified into three main groups called domains; these include the Archaea, the Bacteria, and the Eukarya.
- Prokaryotes arose during the Precambrian Period 3.5 to 3.8 billion years ago.
- Prokaryotic organisms can live in every type of environment on Earth, from very hot, to very cold, to super haline, to very acidic.
- The domains Bacteria and Archaea are the ones containing prokaryotic organisms.
- The Archaea are prokaryotes that inhabit extreme environments, such as inside of volcanoes, while Bacteria are more common organisms, such as *E. coli*.

Key Terms

- **prokaryote**: an organism whose cell (or cells) are characterized by the absence of a nucleus or any other membrane-bound organelles
- **domain**: in the three-domain system, the highest rank in the classification of organisms, above kingdom: Bacteria, Archaea, and Eukarya
- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei, formerly called archaebacteria, but now known to differ fundamentally from bacteria

Evolution of Prokaryotes

In the recent past, scientists grouped living things into five kingdoms (animals, plants, fungi, protists, and prokaryotes) based on several criteria such as: the absence or presence of a nucleus and other membrane-bound organelles, the absence or presence of cell walls, multicellularity, etc. In the late 20th century, the pioneering work of Carl Woese and others compared sequences of small-subunit ribosomal RNA (SSU rRNA) which resulted in a more fundamental way to group organisms on earth. Based on differences in the structure of cell membranes and in rRNA, Woese and his colleagues proposed that all life on earth evolved along three lineages, called domains. The domain Bacteria comprises all organisms in the kingdom Bacteria, the domain Archaea comprises the rest of the prokaryotes, and the domain Eukarya comprises all eukaryotes, including organisms in the kingdoms Animalia, Plantae, Fungi, and Protista.



Figure: **Prokaryotes in extreme environments**: Certain prokaryotes can live in extreme environments such as the Morning Glory pool, a hot spring in Yellowstone National Park. The spring's vivid blue color is from the prokaryotes that thrive in its very hot waters.

The current model of the evolution of the first, living organisms is that these were some form of prokaryotes, which may have evolved out of protobionts. In general, the eukaryotes are thought to have evolved later in the history of life. However, some authors have questioned this conclusion, arguing that the current set of prokaryotic species may have evolved from more complex eukaryotic ancestors through a process of simplification. Others have argued that the three domains of life arose simultaneously, from a set of varied cells that formed a single gene pool.

Two of the three domains, Bacteria and Archaea, are prokaryotic. Based on fossil evidence, prokaryotes were the first inhabitants on Earth, appearing 3.5 to 3.8 billion years ago during the Precambrian Period. These organisms are abundant and ubiquitous; that is, they are present everywhere. In addition to inhabiting moderate environments, they are found in extreme conditions: from boiling springs to permanently frozen environments in Antarctica; from salty environments like the Dead Sea to environments under tremendous pressure, such as the depths of the ocean; and from areas without oxygen, such as a waste management plant, to radioactively-contaminated regions, such as Chernobyl. Prokaryotes reside in the human digestive system and on the skin, are responsible for certain illnesses, and serve an important role in the preparation of many foods.

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8.5C: Phylogenetic Analysis

The molecular approach to microbial phylogenetic analysis revolutionized our thinking about evolution in the microbial world.

Learning Objectives

- Outline the approaches to perform phylogenetic analysis

Key Points

- The purpose of phylogenetic analysis is to understand the past evolutionary path of organisms. Due to technological innovation in modern molecular biology and the rapid advancement in computational science, accurate inference of the phylogeny of a gene or organism seems possible in the near future.
- The developing technology of nucleic acid sequencing, together with the recognition that sequences of building blocks in informational macromolecules can be used as 'molecular clocks' that contain historical information, led to the development of the three- domain model (Archaea – Bacteria -Eucaryota).
- As more genome sequences become available, scientists have found that determining these relationships is complicated by the prevalence of lateral gene transfer among archaea and bacteria.
- Even using improved DNA-based identification methods, the total number of bacterial species is not known and cannot even be estimated with any certainty. Currently, there are a little less than 9,300 known species of prokaryotes.

Key Terms

- **Lateral gene transfer**: Horizontal gene transfer (HGT), also lateral gene transfer (LGT) or transposition refers to the transfer of genetic material between organisms other than vertical gene transfer. Vertical transfer occurs when there is gene exchange from the parental generation to the offspring. LGT is then a mechanism of gene exchange that happens independently of reproduction.
- **microbial phylogenetics**: The study of the evolutionary relatedness among various groups of microorganisms.

Microbial phylogenetics is the study of the evolutionary relatedness among various groups of microorganisms. The molecular approach to microbial phylogenetic analysis revolutionized our thinking about evolution in the microbial world. The purpose of phylogenetic analysis is to understand the past evolutionary path of organisms. Even though we will never know for certain the true phylogeny of any organism, phylogenetic analysis provides best assumptions, thereby providing a framework for various disciplines in microbiology. Due to the technological innovation of modern molecular biology and the rapid advancement in computational science, accurate inference of the phylogeny of a gene or organism seems possible in the near future.

Gene sequences can be used to reconstruct the bacterial phylogeny. These studies indicate that bacteria diverged first from the archaeal/eukaryotic lineage. The term "bacteria" was traditionally applied to all microscopic, single-cell prokaryotes. However, molecular systematics showed prokaryotic life to consist of two separate domains, originally called Eubacteria and Archaebacteria, but now called Bacteria and Archaea that evolved independently from an ancient common ancestor. The archaea and eukaryotes are more closely related to each other than to the bacteria. Due to the relatively recent introduction of molecular systematics and a rapid increase in the number of genome sequences that are available, bacterial classification remains a changing and expanding field. For example, a few biologists argue that the Archaea and Eukaryotes evolved from Gram-positive bacteria.

While morphological or metabolic differences allowed the identification and classification of bacterial strains, it was unclear whether these differences represented variation between distinct species or between strains of the same species. This uncertainty was due to the lack of distinctive structures in most bacteria, as well as lateral gene transfer between unrelated species. The developing technology of nucleic acid sequencing, together with the recognition that sequences of building blocks in informational macromolecules can be used as 'molecular clocks' that contain historical information, led to the development of the three-domain model (Archaea – Bacteria – Eucaryota) in the late 1970's, primarily based on small subunit ribosomal RNA sequence comparisons pioneered by Carl Woese and George Fox.

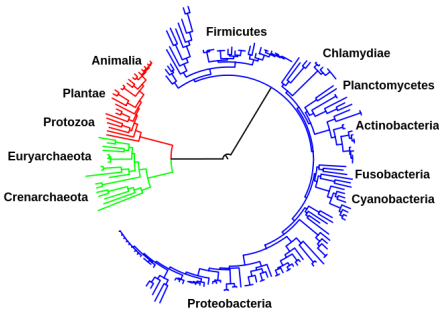

Figure: **Evolutionary tree showing the common ancestry of all three domains of life**: A highly resolved Tree Of Life, based on completely sequenced genomes. Bacteria are colored blue, eukaryotes red, and archaea green. Relative positions of some phyla are shown around the tree.

As more genome sequences become available, scientists have found that determining these relationships is complicated by the prevalence of lateral gene transfer (LGT) among archaea and bacteria. Due to lateral gene transfer, some closely related bacteria can have very different morphologies and metabolisms. To overcome this uncertainty, modern bacterial classification emphasizes molecular systematics, using genetic techniques such as guanine cytosine ratio determination, genome-genome hybridization, as well as sequencing genes that have not undergone extensive lateral gene transfer, such as the rRNA gene.

As with bacterial classification, identification of microorganisms is increasingly using molecular methods. Diagnostics using such DNA-based tools, such as polymerase chain reaction, are increasingly popular due to their specificity and speed, compared to culture-based methods. However, even using these improved methods, the total number of bacterial species is not known and cannot even be estimated with any certainty. Following present classification, there are a little less than 9,300 known species of prokaryotes, which includes bacteria and archaea. but attempts to estimate the true level of bacterial diversity have ranged from 10^7 to 10^9 total species – and even these diverse estimates may be off by many orders of magnitude.

There are four steps in general phylogenetic analysis of molecular sequences: (i) selection of a suitable molecule or molecules (phylogenetic marker), (ii) acquisition of molecular sequences, (iii) multiple sequence alignment (MSA), and (iv) phylogenetic treeing and evaluation.

Multilocus sequence analysis (MLSA) represents the novel standard in microbial molecular systematics. In this context, MLSA is implemented in a relatively straightforward way, consisting essentially in the concatenation of several sequence partitions for the same set of organisms, resulting in a “supermatrix” which is used to infer a phylogeny by means of distance-matrix or optimality criterion-based methods. This approach is expected to have an increased resolving power due to the large number of characters analyzed and a lower sensitivity to the impact of conflicting signals (i.e. phylogenetic incongruence) that result from eventual horizontal gene transfer events. The strategies used to deal with multiple partitions can be grouped in three broad categories: the total evidence, separate analysis, and combination approaches. The concatenation approach that dominates MLSAs in the microbial molecular systematics literature is known to systematists working with plants and animals as the “total molecular evidence” approach. It has been used to solve difficult phylogenetic questions such as the relationships among the major groups of cetaceans, that of microsporidia and fungi, or the phylogeny of major plant lineages. The total molecular evidence approach has been criticized because by directly concatenating all available sequence alignments. The evidence of conflicting phylogenetic signals in the different data partitions is lost along with the possibility to uncover the evolutionary processes that gave rise to such contradictory signals.

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8.5D: Nongenetic Categories for Medicine and Ecology

In medicine, microorganisms are identified by morphology, physiology, and other attributes; in ecology by habitat, energy, and carbon source.

Learning Objectives

- Outline the traits used to classify: bacteria, viruses and microrganisms in ecology

Key Points

- A pathogen causes disease in its host. In medicine, there are several broad types of pathogens: viruses, bacteria, fungi, eukaryotic parasites, and prions.
- When identifying bacteria in the laboratory, the following characteristics are used: Gram staining, shape, presence of a capsule, bonding tendency, motility, respiration, growth medium, and whether it is intra- or extracellular.
- Viruses are mainly classified by phenotypic characteristics, such as morphology, nucleic acid type, mode of replication, host organisms, and the type of disease they cause.
- In ecology, microorganisms are classified by the type of habitat they require, or trophic level, energy source and carbon source.
- Biologists have found that microbial life has an amazing flexibility for surviving in extreme environments that would be completely inhospitable to complex organisms; these are called extremophiles and many kinds exist.
- Different species of microorganisms use a mix of different sources of energy and carbon. These may be alternations between photo- and chemotrophy, between litho- and organotrophy, between auto- and heterotrophy or a combination of them.

Key Terms

- **obligate**: Able to exist or survive only in a particular environment or by assuming a particular role: an obligate parasite; an obligate anaerobe.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.
- **extremophile**: An organism that lives under extreme conditions of temperature, salinity, and so on. They are commercially important as a source of enzymes that operate under similar conditions.

Classifying microorganisms in medicine

A pathogen (colloquially known as a germ) is an infectious agent that causes disease in its host. In medicine, there are several broad types of pathogens: viruses, bacteria, fungi, eukaryotic parasites, and prions.

BACTERIA

Although most bacteria are harmless, even beneficial, quite a few are pathogenic. Each pathogenic species has a characteristic spectrum of interactions with its human hosts.

Conditionally, pathogenic bacteria are only pathogenic under certain conditions; such as a wound that allows for entry into the blood, or a decrease in immune function. Bacterial infections can also be classified by location in the body, for example, the vagina, lungs, skin, spinal cord and brain, and urinary tract.

When identifying bacteria in the laboratory, the following chatacteristics are used: Gram staining, shape, presence of a capsule, bonding tendency (singly or in pairs), motility, respiration, growth medium, and whether it is intra- or extracellular.

Culture techniques are designed to grow and identify particular bacteria, while restricting the growth of the others in the sample. Often these techniques are designed for specific specimens: for example, a sputum sample will be treated to identify organisms that cause pneumonia. Once a pathogenic organism has been isolated, it can be further characterised by its morphology, growth patterns (aerobic or anaerobic), patterns of hemolysis, and staining.

VIRUSES

Similar to the classification systems used for cellular organisms, virus classification is the subject of ongoing debate due to their pseudo-living nature. Essentially, they are non-living particles with some chemical characteristics similar to those of life; thus, they

do not fit neatly into an established biological classification system.

Viruses are mainly classified by phenotypic characteristics,such as:

- morphology
- nucleic acid type
- mode of replication
- host organisms
- type of disease they cause

Currently there are two main schemes used for the classification of viruses: (1) the International Committee on Taxonomy of Viruses (ICTV) system; and (2) the Baltimore classification system, which places viruses into one of seven groups. To date, six orders have been established by the ICTV:

- Caudovirales
- Herpesvirales
- Mononegavirales
- Nidovirales
- Picornavirales
- Tymovirales

These orders span viruses with varying host ranges, only some of which infect human hosts.

Baltimore classification is a system that places viruses into one of seven groups depending on a combination of:

- their nucleic acid (DNA or RNA)
- strandedness (single or double)
- sense
- method of replication

Other classifications are determined by the disease caused by the virus or its morphology, neither of which is satisfactory as different viruses can either cause the same disease or look very similar. In addition, viral structures are often difficult to determine under the microscope. Classifying viruses according to their genome means that those in a given category will all behave in a similar fashion, offering some indication of how to proceed with further research.

Other organisms invariably cause disease in humans, such as obligate intracellular parasites that are able to grow and reproduce only within the cells of other organisms.

CATEGORIES OF MICROORGANISMS IN ECOLOGY

In ecology, microorganisms are classified by the type of habitat they require, or trophic level, energy source and carbon source.

Habitat Type

Biologists have found that microbial life has an amazing flexibility for surviving in extreme environments that would be completely inhospitable to complex organisms. Some even concluded that life may have begun on Earth in hydrothermal vents far under the ocean's surface.

An *extremophile* is an organism that thrives in physically or geochemically extreme conditions, detrimental to most life on Earth. Most known extremophiles are microbes. The domain *Archaea* contains renowned examples, but extremophiles are present in numerous and diverse genetic lineages of both bacteria and archaeans. In contrast, organisms that live in more moderate environments may be termed *mesophiles* or *neutrophiles*.

There are many different classes of extremophiles, each corresponding to the way its environmental niche differs from mesophilic conditions. Many extremophiles fall under multiple categories and are termed *polyextremophiles*. Some examples of types of extremophiles:

- *Acidophile*: an organism with optimal growth at levels of pH 3 or below
- *Xerophile*: an organism that can grow in extremely dry, desiccating conditions; exemplified by the soil microbes of the Atacama Desert
- *Halophile*: an organism requiring at least 0.2M concentrations of salt (NaCl) for growth
- *Thermophile*: an organism that can thrive at temperatures between 45–122 °C

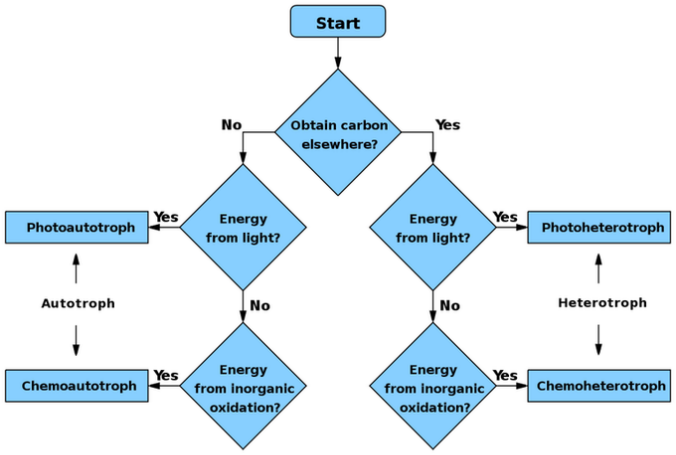

Figure: **The nutritional modes of an organism**: A flowchart to determine if a species is autotroph, heterotroph, or a subtype.

- *Phototrophs*: carry out photon capture to acquire energy. They use the energy from light to carry out various cellular metabolic processes. They are not obligatorily photosynthetic. Most of the well-recognized phototrophs are *autotrophs*, also known as *photoautotrophs*, and can fix carbon.
- *Photoheterotrophs*: produce ATP through photophosphorylation but use environmentally-obtained organic compounds to build structures and other bio- molecules.
- *Photolithoautotroph*: an autotrophic organism that uses light energy, and an inorganic electron donor (e.g., H_2O, H_2, H_2S), and CO_2 as its carbon source.
- *Chemotrophs*: obtain their energy by the oxidation of electron donors in their environments.
- *Chemoorganotrophs*: organisms which oxidize the chemical bonds in organic compounds as their energy source and attain the carbon molecules they need for cellular function. These oxidized organic compounds include sugars, fats and proteins.
- *Chemoorganoheterotrophs* (or organotrophs) exploit reduced-carbon compounds as energy sources, such as carbohydrates, fats, and proteins from plants and animals. *Chemolithoheterotrophs* (or *lithotrophic heterotrophs*) utilize inorganic substances to produce ATP, including hydrogen sulfide and elemental sulfur.
- *Lithoautotroph*: derives energy from reduced compounds of mineral origin. May also be referred to as *chemolithoautotrophs*, reflecting their autotrophic metabolic pathways. Lithoautotrophs are exclusively microbes and most are bacteria. For lithoautotrophic bacteria, only inorganic molecules can be used as energy sources.
- *Mixotroph*: Can use a mix of different sources of energy and carbon. These may be alternations between photo- and chemotrophy, between litho- and organotrophy, between auto- and heterotrophy or a combination of them. Can be either eukaryotic or prokaryotic.

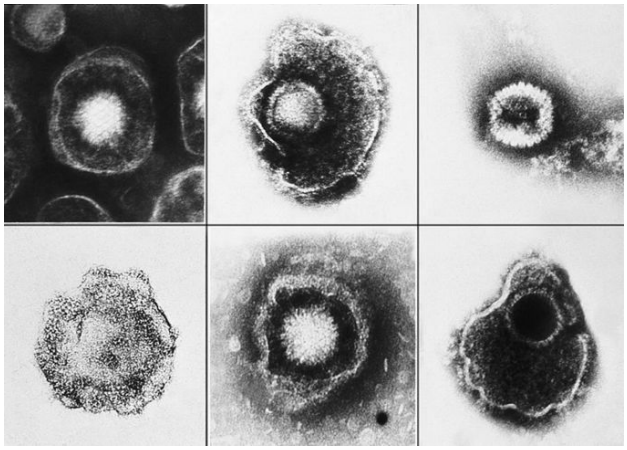

Figure: **Differing morphology in different Herpes viruses**: Various viruses from the Herpesviridae family seen using an electron micrograph. Amongst these members is varicella-zoster (Chickenpox), and herpes simplex type 1 and 2 (HSV-1, HSV-2).

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SECTION OVERVIEW

8.6: Bacterial Diversity

Topic hierarchy

8.6A: Common Bacterial Traits

8.6C: Unclassified and Uncultured Bacteria

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8.6A: Common Bacterial Traits

Bacteria are a subset of prokaryotes and while very different, they still have some common features.

Learning Objectives

- Identify common bacterial traits

Key Points

- Bacteria vary from species to species, thus assigning many common traits to bacteria is difficult. Bacterial species are typified by their diversity.
- There are three notable common traits of bacteria, 1) lack of membrane-bound organelles, 2) unicellular and 3) small (usually microscopic) size.
- Not all prokaryotes are bacteria, some are archaea, which although they share common physicals features to bacteria, are ancestrally different from bacteria.

Key Terms

- **archaea**: a taxonomic domain of single-celled organisms lacking nuclei, formerly called archaebacteria but now known to differ fundamentally from bacteria.
- **binary fission**: a form of asexual reproduction and cell division used by all prokaryotes, (bacteria and archaebacteria)

Bacteria constitute a large domain of prokaryotic microorganisms. Bacteria were among the first life forms to appear on Earth, and are present in most habitats on the planet. Bacteria grow in soil, acidic hot springs, radioactive waste, water, and deep in the Earth's crust. In addition, they grow in organic matter and the live bodies of plants and animals, providing outstanding examples of mutualism in the digestive tracts of humans, termites, and cockroaches.

But what defines a bacteria? Bacteria as prokaryotes share many common features, such as:

1. A lack of membrane-bound organelles
2. Unicellularity and thus division by binary-fission
3. Generally small size

Bacteria do not tend to have membrane-bound organelles in their cytoplasm and thus contain few large intracellular structures. They consequently lack a true nucleus, mitochondria, chloroplasts, and the other organelles present in eukaryotic cells, such as the Golgi apparatus and endoplasmic reticulum. Bacteria were once seen as simple bags of cytoplasm, but elements such as prokaryotic cytoskeleton, and the localization of proteins to specific locations within the cytoplasm have been found to show levels of complexity. These subcellular compartments have been called "bacterial hyperstructures".

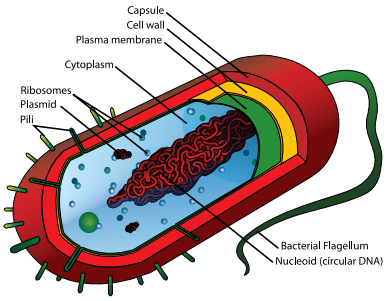

Figure: **Bacterial structures**: Cell structure of a Gram-positive prokaryote.

Unlike in multicellular organisms, increases in cell size (cell growth and reproduction by cell division) are tightly linked in unicellular organisms. Bacteria grow to a fixed size and then reproduce through binary fission, a form of asexual reproduction.

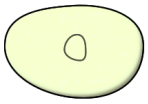

Figure: **Binary fission**: Many bacteria reproduce through binary fission.

Perhaps the most obvious structural characteristic of bacteria is (with some exceptions) their small size. For example, Escherichia coli cells, an “average” sized bacterium, are about 2 micrometres (μm) long and 0.5 μm in diameter. Small size is extremely important because it allows for a large surface area-to-volume ratio which allows for rapid uptake and intracellular distribution of nutrients and excretion of wastes.

The term “bacteria” was traditionally applied to all microscopic, single-cell prokaryotes, having the similar traits outlined above. However, molecular systematics show prokaryotic life to consist of two separate domains, originally called Eubacteria and Archaebacteria, but now called Bacteria and Archaea that evolved independently from an ancient common ancestor. The archaea and eukaryotes are more closely related to each other than either is to the bacteria. It should be noted that Bacteria and Archaea are similar physically, but have different ancestral origins as determined by DNA of the genomes that encode different prokaryotes.

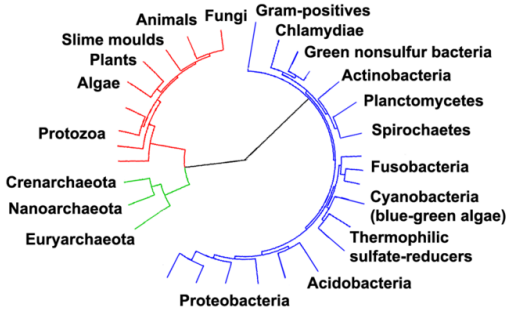

Figure: **Archaea and other domains**: Phylogenetic tree showing the relationship between the Archaea and other domains of life. Eukaryotes are colored red, archaea green and bacteria blue.

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8.6C: Unclassified and Uncultured Bacteria

To classify a species of bacteria, one usually needs to isolate and grow up the species that is to be classified.

Learning Objectives

- Estimate bacterial diversity

Key Points

- Classification is the attempt to identify and group different species of bacteria together by common traits.
- If a bacterium cannot be cultured, it is hard to study it to find commonalities and differences from other species of bacteria.
- Recent advances in molecular technique are allowing uncultured bacteria to be classified.

Key Terms

- **viable but nonculturable**: Viable but nonculturable (VBNC) bacteria refers to bacteria that are in a state of very low metabolic activity and do not divide, but are alive and have the ability to become culturable once resuscitated.

Describing Diversity

Classification seeks to describe the diversity of bacterial species by naming and grouping organisms based on similarities. Bacteria can be classified on the basis of cell structure, cellular metabolism, or by differences in cell components such as DNA, fatty acids, pigments, antigens, and quinones.

While these schemes previously allowed the identification and classification of bacterial strains, it was long unclear whether these differences represented variation between distinct species or between strains of the same species. This uncertainty resulted from the lack of distinctive structures in most bacteria, as well as lateral gene transfer that occurred between unrelated species. Because of the existence of lateral gene transfer, some closely related bacteria have very different morphologies and metabolisms.

To overcome these uncertainties, modern bacterial classification emphasizes molecular systematics, using genetic techniques such as guanine cytosine ratio determination, genome-genome hybridization, as well as sequencing genes that have not undergone extensive lateral gene transfer, such as the rRNA gene.

Uni-Species Cultures for Identification

While there are several molecular tools that allow us to classify or distinguish different bacterial species, this is predicated on obtaining uni-species cultures of a given bacteria. Culture techniques are designed to promote the growth and identify particular bacteria, while restricting the growth of the other bacteria in the sample. Often these techniques are designed for specific specimens; for example, a sputum sample will be treated to identify organisms that cause pneumonia, while stool specimens are cultured on selective media to identify organisms that cause diarrhoea while preventing growth of non- pathogenic bacteria. Specimens that are normally sterile, such as blood, urine, or spinal fluid, are cultured under conditions designed to grow all possible organisms. Once a pathogenic organism has been isolated, it can be further characterized by its morphology, by growth patterns such as aerobic or anaerobic growth, by patterns of hemolysis and by staining. If a bacteria can not be cultured, classification can prove to be very difficult.

DNA Sequencing

However, recent advances in molecular techniques do allow the sequencing of DNA from bacterial species, without the reliance on a pure culture of that given bacteria. Diagnostics using such DNA-based tools, such as polymerase chain reaction, are increasingly popular due to their specificity and speed, compared to culture-based methods. These methods also allow the detection and identification of “viable but nonculturable” cells that are metabolically active but non-dividing, which can be applied to isolates of bacterial species that cannot be cultured. However, even using these improved methods, the total number of bacterial species is not known and cannot even be estimated with any certainty. Following present classification, there are a little less than 9,300 known species of prokaryotes, which includes bacteria and archaea. Attempts to estimate the true level of bacterial diversity have ranged from 10^7 to 10^9 total species – and even these diverse estimates may be off by many orders of magnitude.

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SECTION OVERVIEW

8.7: Proteobacteria

Topic hierarchy

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8.7B: Alphaproteobacteria

8.7C: Betaproteobacteria

8.7D: Morphologically Unusual Proteobacteria

8.7E: Gammaproteobacteria

8.7F: Deltaproteobacteria

8.7G: Epsilonproteobacteria

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8.7A: Overview of Proteobacteria

The Proteobacteria are a major group (phylum) of bacteria.

Learning Objectives

- Categorize proteobacteria

Key Points

- Proteobacteria include a wide variety of pathogens, such as Escherichia, Salmonella, Vibrio, Helicobacter, and many other notable genera.
- All proteobacteria are Gram-negative, with an outer membrane mainly composed of lipopolysaccharides.
- The divisions of the proteobacteria include: Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Deltaproteobacteria, Epsilonproteobacteria and Zetaproteobacteria.

Key Terms

- **Proteobacteria**: The Proteobacteria are a major group (phylum) of bacteria. They include a wide variety of pathogens, such as Escherichia, Salmonella, Vibrio, Helicobacter, and many other notable genera. Others are free-living, and include many of the bacteria responsible for nitrogen fixation.
- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.
- **Gram-negative**: Gram-negative bacteria are bacteria that do not retain crystal violet dye in the Gram staining protocol. In a Gram stain test, a counterstain (commonly safranin) is added after the crystal violet, coloring all Gram-negative bacteria with a red or pink color.

The Proteobacteria are a major group (phylum) of bacteria. They include a wide variety of pathogens, such as Escherichia, Salmonella, Vibrio, Helicobacter, and many other notable genera. Others are free-living, and include many of the bacteria responsible for nitrogen fixation.

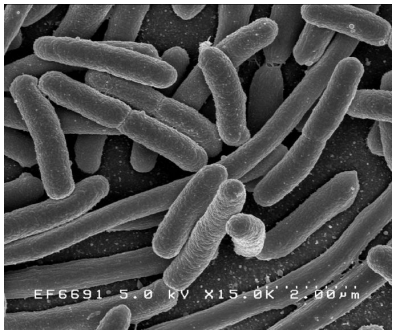

Figure: **Classification of E. coli**: Domain: Bacteria, Kingdom: Eubacteria, Phylum: Proteobacteria, Class: Gammaproteobacteria, Order: Enterobacteriales, Family: Enterobacteriaceae, Genus: Escherichia, Species: E. coli.

In 1987, Carl Woese established this grouping, and informally called it the “purple bacteria and their relatives”. Because of the great diversity of forms found in this group, the Proteobacteria are named after Proteus, a Greek god of the sea, capable of assuming many different shapes, and it is therefore not named after the genus Proteus.

All proteobacteria are Gram-negative, with an outer membrane mainly composed of lipopolysaccharides. Many move about using flagella, but some are nonmotile or rely on bacterial gliding. The last include the myxobacteria, a unique group of bacteria that can aggregate to form multicellular fruiting bodies. There is also a wide variety in the types of metabolism. Most members are facultatively or obligately anaerobic, chemoautotrophs, and heterotrophic, but there are numerous exceptions. A variety of genera, which are not closely related to each other, convert energy from light through photosynthesis. These are called purple bacteria, referring to their mostly reddish pigmentation.

The group is defined primarily in terms of ribosomal RNA (rRNA) sequences. The Proteobacteria are divided into six sections, referred to by the Greek letters alpha through zeta, again based on rRNA sequences. These are often treated as classes. The alpha,

beta, delta, epsilon sections are monophyletic, but the Gammaproteobacteria due to the Acidithiobacillus genus is paraphyletic to Betaproteobacteria, according to multigenome alignment studies, which if done correctly are more precise than 16S (note that Mariprofundus ferrooxydans sole member of the Zetaproteobacteria was previously misclassified on NCBI taxonomy). Acidithiobacillus contains 5 species and the sole genus in its order Acidithiobacillales.

The divisions of the proteobacteria were once regarded as subclasses (e.g. α-subclass of the Proteobacteria), but are now regarded as classes (e.g. the Alphaproteobacteria). These classes include: Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Deltaproteobacteria, Epsilonproteobacteria and Zetaproteobacteria.

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8.7B: Alphaproteobacteria

Learning Objectives

- Describe the Alphaproteobacteria class of Proteobacteria

Alphaproteobacteria is a class of Proteobacteria. Like all Proteobacteria, they are Gram-negative. The Alphaproteobacteria comprise most phototrophic genera, but also several genera metabolising C1-compounds (e.g., Methylobacterium spp.), symbionts of plants (e.g., Rhizobium spp.) and animals, and a group of pathogens, the Rickettsiaceae. In addition, the precursors of the mitochondria of eukaryotic cells are thought to have originated from Rickettsia spp. (See endosymbiotic theory.). Because of their symbiotic properties, scientists often use Alphaproteobacteria of the genus Agrobacterium to transfer foreign DNA into plant genomes, and they also have many other biotechnological properties. Aerobic anoxygenic phototrophic bacteria are alphaproteobacteria, widely distributed marine plankton that may constitute over 10% of the open ocean microbial community.

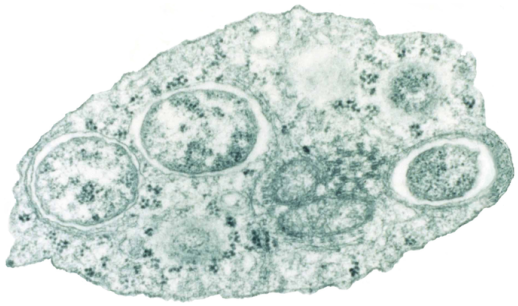

Figure: ***Alphaproteobacteria****: Transmission electron micrograph of Wolbachia within an insect cell.*

The Class Alphaproteobacteria comprises ten orders (viz. Magnetococcales, Rhodobacterales, Rhodospirillales, Rickettsiales, Sphingomonadales, Caulobacterales, Kiloniellales, Kordiimonadales, Parvularculales and Sneathiellales).

Comparative analyses of the sequenced genomes have also led to discovery of many conserved indels in widely distributed proteins and whole proteins (i.e. signature proteins) that are distinctive characteristics of either all Alphaproteobacteria, or their different main orders (viz. Rhizobiales, Rhodobacterales, Rhodospirillales, Rickettsiales, Sphingomonadales and Caulobacterales) and families (viz. Rickettsiaceae, Anaplasmataceae, Rhodospirillaceae, Acetobacteraceae, Bradyrhiozobiaceae, Brucellaceae and Bartonellaceae).

These molecular signatures provide novel means for the circumscription of these taxonomic groups and for identification/assignment of new species into these groups. Phylogenetic analyses and conserved indels in large numbers of other proteins provide evidence that Alphaproteobacteria have branched off later than most other phyla and Classes of Bacteria with the exception of Betaproteobacteria and Gammaproteobacteria.

The currently accepted taxonomy is based on the List of Prokaryotic names with Standing in Nomenclature (LPSN) and National Center for Biotechnology Information (NCBI) and the phylogeny is based on 16S rRNA-based LTP release 106 by 'The All-Species Living Tree' Project.

Key Points

- The Class Alphaproteobacteria comprises ten orders (viz. Magnetococcales, Rhodobacterales, Rhodospirillales, Rickettsiales, Sphingomonadales, Caulobacterales, Kiloniellales, Kordiimonadales, Parvularculales and Sneathiellales).
- The Alphaproteobacteria comprise most phototrophic genera, but also several genera metabolising C1-compounds (e.g., Methylobacterium spp.), symbionts of plants (e.g., Rhizobium spp.) and animals, and a group of pathogens, the Rickettsiaceae.
- Scientists often use Alphaproteobacteria of the genus Agrobacterium to transfer foreign DNA into plant genomes.

Key Terms

- **Alphaproteobacteria**: Alphaproteobacteria is a class of Proteobacteria that are Gram-negative.
- **phototroph**: An organism that carries out photon capture to acquire energy. They use the energy from light to carry out various cellular metabolic processes.
- **C1-compounds**: chemical compounds containing only one carbon atom, for example, methanol.

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8.7C: Betaproteobacteria

Learning Objectives

- Evaluate the importance of Betaproteobacteria

Betaproteobacteria is a class of Proteobacteria that are all Gram-negative. The Betaproteobacteria consist of several groups of aerobic or facultative bacteria that are often highly versatile in their degradation capacities, but also contain *chemolithotrophic* genera (e.g., the ammonia-oxidising genus *Nitrosomonas*) and some phototrophs (members of the genera *Rhodocyclus* and *Rubrivivax*).

Nitrosomonas is a genus comprising rod shaped chemoautotrophic bacteria. This rare bacteria oxidizes ammonia into nitrite as a metabolic process. *Nitrosomonas* are useful in treatment of industrial and sewage waste and in the process of bioremediation. They play an important role in the nitrogen cycle by increasing the availability of nitrogen to plants while limiting carbon dioxide fixation.

Betaproteobacteria play a role in nitrogen fixation in various types of plants, oxidizing ammonium to produce nitrite- an important chemical for plant function. Many of them are found in environmental samples, such as waste water or soil. Pathogenic species within this class are the *Neisseriaceae* (gonorrhea and meningitis) and species of the genus *Burkholderia*.



Figure: ***Betaproteobacteria****: Burkholderia pseudomallei colonies on a Blood agar plate.*

Burkholderia is a genus of proteobacteria probably best known for its pathogenic members: *Burkholderia mallei*, responsible for glanders, a disease that occurs mostly in horses and related animals; *Burkholderia pseudomallei*, causative agent of *melioidosis*; and *Burkholderia cepacia*, an important pathogen of pulmonary infections in people with cystic fibrosis (CF). The *Burkholderia* (previously part of *Pseudomonas*) genus name refers to a group of virtually ubiquitous gram-negative, motile, obligately aerobic rod-shaped bacteria including both animal/human (see above) and plant pathogens as well as some environmentally important species.

The currently accepted taxonomy is based on the List of Prokaryotic names with Standing in Nomenclature (LPSN) and National Center for Biotechnology Information (NCBI) and the phylogeny is based on 16S rRNA-based LTP release 106 by 'The All-Species Living Tree' Project.

Key Points

- The Betaproteobacteria consist of several groups of aerobic or facultative bacteria that are often highly versatile in their degradation capacities.
- The Betaproteobacteria contain chemolithotrophic genera (e.g., the ammonia-oxidising genus Nitrosomonas) and some phototrophs (members of the genera Rhodocyclus and Rubrivivax).
- Betaproteobacteria play a role in nitrogen fixation in various types of plants, oxidizing ammonium to produce nitrite- an important chemical for plant function.

Key Terms

- **Betaproteobacteria**: Betaproteobacteria is a class of Proteobacteria. Betaproteobacteria are, like all Proteobacteria, Gram-negative.

- **glanders**: An infectious disease of horses, mules and donkeys caused by the bacterium Burkholderia, one species of which may be transmitted to humans.
- **melioidosis**: An infectious disease caused by a Gram-negative bacterium, Burkholderia pseudomallei, found in soil and water. It is endemic in Southeast Asia and northern Australia. Symptoms may include pain in chest, bones, or joints; cough; skin infections, lung nodules and pneumonia.

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8.7D: Morphologically Unusual Proteobacteria

Learning Objectives

- Compare the two main groups of morphologically unusual proteobacteria

Two main groups of morphologically unusual proteobacteria include spirillum and prosthecate bacteria. Spirillum in microbiology refers to a bacterium with a cell body that twists like a spiral. It is a genus comprising elongated forms with clusters of flagellae at both poles. Spirillium usually live in stagnant water rich in organic matter. They are twisted and aerobic, and are highly flexible, like a spring.

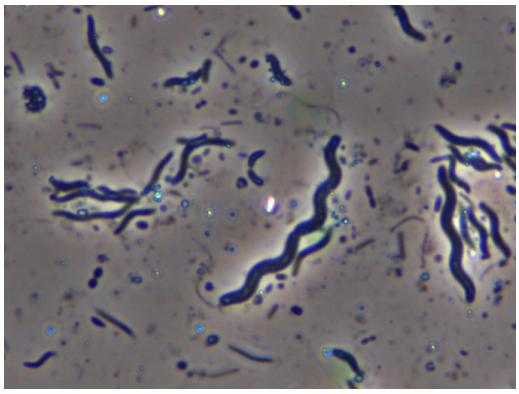

Figure: ***Spirillum****: Spirillum in microbiology refers to a bacterium with a cell body that twists like a spiral.*

Prosthecate bacteria are a non-phylogenetically related group of Gram-negative bacteria that possess appendages, termed prosthecae. These cellular appendages are neither pili nor flagella, as they are extensions of the cellular membrane and contain cytosol. Prosthecates are generally chemoorganotrophic aerobes that can grow in nutrient-poor habitats, being able to survive at nutrient levels on the order of parts-per-million – for which reason they are often found in aquatic habitats. These bacteria will attach to surfaces with their prosthecae, allowing a greater surface area with which to take up nutrients (and release waste products). Some prosthecates will grow in nutrient-poor soils as aerobic heterotrophs.

Caulobacter: An Important Model Organism

One notable group of prosthecates is the genus Caulobacter crescentus, a Gram-negative, oligotrophic bacterium widely distributed in fresh water lakes and streams. Caulobacter is an important model organism for studying the regulation of the cell cycle, asymmetric cell division, and cellular differentiation. Caulobacter daughter cells have two very different forms. One daughter is a mobile “swarmer” cell that has a single flagellum at one cell pole that provides swimming motility for chemotaxis. The other daughter, called the “stalked” cell, has a tubular stalk structure protruding from one pole that has an adhesive holdfast material on its end, with which the stalked cell can adhere to surfaces. Swarmer cells differentiate into stalked cells after a short period of motility. Chromosome replication and cell division only occurs in the stalked cell stage. The second word of its name (*crescentus)* refers to the fact that it forms a crescent shape; crescentin is a protein that imparts this shape.

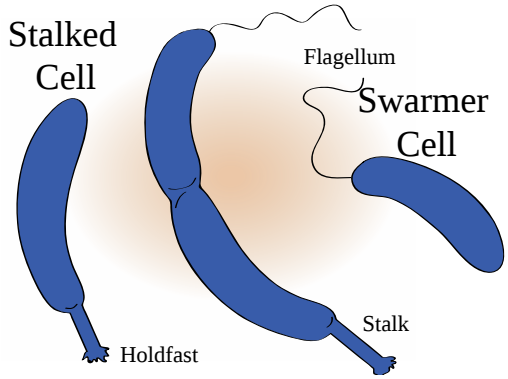

Figure: ***Caulobacter crescentus****: Caulobacter daughter cells have two very different forms. One daughter is a mobile "swarmer" cell that has a single flagellum at one cell pole that provides swimming motility for chemotaxis. The other daughter, called the "stalked" cell has a tubular stalk structure protruding from one pole that has an adhesive holdfast material on its end, with which the stalked cell can adhere to surfaces. Swarmer cells differentiate into stalked cells after a short period of motility.*

Key Points

- Spirillum in microbiology refers to a bacterium with a cell body that twists like a spiral.
- Prosthecate bacteria are a non-phylogenetically related group of Gram-negative bacteria that possess appendages, termed prosthecae.
- Caulobacter is an important model organism for studying the regulation of the cell cycle, asymmetric cell division, and cellular differentiation.

Key Terms

- **spirillum**: Any of various aerobic bacteria of the genus Spirillum, having an elongated spiral form and bearing a tuft of flagella.
- **morphologically**: In biology, morphology is a branch of bioscience dealing with the study of the form and structure of organisms and their specific structural features.
- **prosthecate**: Prosthecate bacteria are a non-phylogenetically related group of Gram-negative bacteria that possess appendages, termed prosthecae. These cellular appendages are neither pili nor flagella, as they are extensions of the cellular membrane and contain cytosol. One notable group of prosthecates is the genus Caulobacter.

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8.7E: Gammaproteobacteria

Learning Objectives

- Classify Gammaproteobacteria

Gammaproteobacteria is a class of several medically, ecologically and scientifically important groups of bacteria, such as the Enterobacteriaceae (Escherichia coli), Vibrionaceae and Pseudomonadaceae. Like all Proteobacteria, the Gammaproteobacteria are Gram-negative.

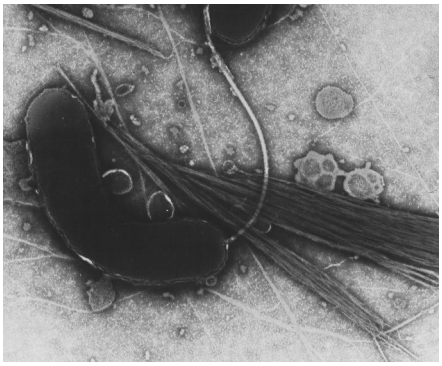

Figure: ***Gammaproteobacteria****: Transmission electron microsope image of Vibrio choleraethat has been negatively stained. Vibrio choleraeis the bacteria responsible for the gastroinestinal disease cholera. In order to get the disease cholera, the bacteria must be able to colonize in the small intestine and a critical factor necessary for this colonization is the toxin-co-regulated pilus(TCP). 0395 is a wild type strain, showing the normal bundling of toxin-co-regulated pilus(TCP). Wild-type pili are clearly visible as 7 nm fibres that form bundles @ 0.2Ð0.3 µm wide and 3Ð6 µm long.*

The Gammaproteobacteria comprise several medically and scientifically important groups of bacteria, such as the Enterobacteriaceae, Vibrionaceae and Pseudomonadaceae. A number of important pathogens belongs to this class, e.g. Salmonella spp. (enteritis and typhoid fever), Yersinia pestis (plague), Vibrio cholerae (cholera), Pseudomonas aeruginosa (lung infections in hospitalized or cystic fibrosis patients), and Escherichia coli (food poisoning).

The Enterobacteriaceae is a large family of Gram-negative bacteria that includes, along with many harmless symbionts, many of the more familiar pathogens, such as Salmonella, Escherichia coli, Yersinia pestis, Klebsiella and Shigella. Other disease-causing bacteria in this family include Proteus, Enterobacter, Serratia, and Citrobacter. This family is the only representative in the order Enterobacteriales of the class Gammaproteobacteria in the phylum Proteobacteria. Phylogenetically, in the Enterobacteriales, several peptidoglycan-less insect endosymbionts form a sister clade to the Enterobacteriaceae, but since they are not validly described, this group is not officially a taxon; examples of these species are Sodalis, Buchnera, Wigglesworthia, Baumannia and Blochmannia. Members of the Enterobacteriaceae can be trivially referred to as enterobacteria, as several members live in the intestines of animals. In fact, the etymology of the family is enterobacterium with the suffix to designate a family (aceae) — not after the genus Enterobacter (which would be “Enterobacteraceae”)— and the type genus is Escherichia.

Members of Chromatium are photosynthetic and oxidize hydrogen sulfide instead of water, producing sulfur as excrement. Some Gammaproteobacteria are methane oxidizers, and many of them are in symbiosis with geothermic ocean vent dwelling animals.

Key Points

- Gammaproteobacteria include an exceeding number of important pathogens, e.g. Salmonella, Yersinia, Vibrio, Pseudomonas aeruginosa.
- Like all Proteobacteria, the Gammaproteobacteria are Gram-negative.
- Some Gammaproteobacteria are methane oxidizers, and many of them are in symbiosis with geothermic ocean vent dwelling animals.

Key Terms

- **symbiosis**: A close, prolonged association between two or more organisms of different species, regardless of benefit to the members.

- **pathogens**: A pathogen or infectious agent (colloquially known as a germ) is a microorganism (in the widest sense, such as a virus, bacterium, prion, or fungus) that causes disease in its host. The host may be an animal (including humans), a plant, or even another microorganism.
- **Gammaproteobacteria**: Gammaproteobacteria is a class of several medically, ecologically and scientifically important groups of bacteria, such as the Enterobacteriaceae (Escherichia coli), Vibrionaceae and Pseudomonadaceae. Like all Proteobacteria, the Gammaproteobacteria are Gram-negative.

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8.7F: Deltaproteobacteria

Deltaproteobacteria is a class of Proteobacteria that are Gram-negative.

Learning Objectives

- Review the Deltaproteobacteria class of Proteobacteria

Key Points

- The Deltaproteobacteria comprise a branch of predominantly aerobic genera.
- Deltaproteobacteria include the fruiting-body-forming Myxobacteria which release myxospores in unfavorable environments.
- Deltaproteobacteria include a branch of strictly anaerobic genera, which contains most of the known sulfate- (Desulfovibrio, Desulfobacter, Desulfococcus, Desulfonema, etc.) and sulfur-reducing bacteria (e.g. Desulfuromonas spp.).

Key Terms

- **aerobic**: Living or occurring only in the presence of oxygen.
- **Deltaproteobacteria**: Deltaproteobacteria is a class of Proteobacteria. All species of this group are, like all Proteobacteria, Gram-negative.
- **Gram-negative**: Gram-negative bacteria are bacteria that do not retain crystal violet dye in the Gram staining protocol. In a Gram stain test, a counterstain (commonly safranin) is added after the crystal violet, coloring all Gram-negative bacteria with a red or pink color.

Deltaproteobacteria is a class of Proteobacteria. All species of this group are, like all Proteobacteria, Gram-negative.

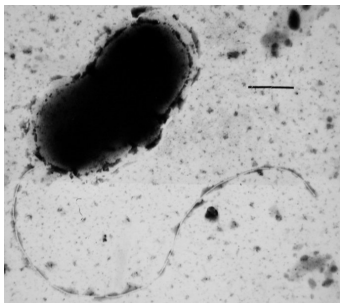

Figure: **Deltaproteobacteria**: Desulfovibrio vulgaris

The Deltaproteobacteria comprise a branch of predominantly aerobic genera, the fruiting-body-forming Myxobacteria that release myxospores in unfavorable environments. It is a branch of strictly anaerobic genera, which contains most of the known sulfate- (Desulfovibrio, Desulfobacter, Desulfococcus, Desulfonema, etc.) and sulfur-reducing bacteria (e.g. Desulfuromonas spp.) alongside several other anaerobic bacteria with different physiology (e.g. ferric iron-reducing Geobacter spp. and syntrophic Pelobacter and Syntrophus spp.). A pathogenic intracellular Deltaproteobacteria has recently been identified.

The myxobacteria (“slime bacteria”) are a group of bacteria that predominantly live in the soil and feed on insoluble organic substances. The myxobacteria have very large genomes, relative to other bacteria, e.g. 9–10 million nucleotides. Sorangium cellulosum has the largest known (as of 2008) bacterial genome, at 13.0 million nucleotides. Myxobacteria are included among the delta group of proteobacteria, a large taxon of Gram-negative forms.

Myxobacteria can move actively by gliding. They typically travel in swarms (also known as wolf packs), containing many cells kept together by intercellular molecular signals. Individuals benefit from aggregation as it allows accumulation of extracellular enzymes which are used to digest food. This in turn increases feeding efficiency. Myxobacteria produce a number of biomedically and industrially useful chemicals, such as antibiotics. They export those chemicals outside of the cell.

The currently accepted taxonomy is based on the List of Prokaryotic Names with Standing in Nomenclature (LPSN) and National Center for Biotechnology Information (NCBI) and the phylogeny is based on 16S rRNA-based LTP release 106 by ‘The All-Species Living Tree’ Project.

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8.7G: Epsilonproteobacteria

Learning Objectives

- Identify the characteristics of Epsilonproteobacteria

Epsilonproteobacteria is a class of Proteobacteria. All species of this class are, like all Proteobacteria, Gram-negative.



Figure: ***Epsilonproteobacteria****: Campylobacter bacteria are the number-one cause of food-related gastrointestinal illness in the United States. To learn more about this pathogen, ARS scientists are sequencing multiple Campylobacter genomes. This scanning electron microscope image shows the characteristic spiral, or corkscrew, shape of C. jejuni cells and related structures.*

The Epsilonproteobacteria consist of few known genera, mainly the curved to spirilloid Wolinella spp., Helicobacter spp., and Campylobacter spp. Most of the known species inhabit the digestive tract of animals and serve as symbionts (Wolinella spp. in cows) or pathogens (Helicobacter spp. in the stomach, Campylobacter spp. in the duodenum).

There have also been numerous environmental sequences of Epsilonproteobacteria recovered from hydrothermal vents and cold seep habitats. A member of the class Epsilonproteobacteria occurs as an endosymbiont in the large gills of the deep water sea snail *Alviniconcha hessleri*. Often the epsilonproteobacteria living in hydrothermal deep sea-vents exhibit chemolithotrophic features, and they are able to meet their energy needs by reducing or oxidixing chemical compounds.

Helicobacter

Helicobacter is a genus of Gram-negative bacteria possessing a characteristic helix shape. They were initially considered to be members of the Campylobacter genus, but since 1989 they have been grouped in their own genus. The Helicobacter genus belongs to the class Epsilonproteobacteria, order Campylobacterales, family Helicobacteraceae and already has more than 35 species.

Some species have been found living in the lining of the upper gastrointestinal tract, as well as the liver of mammals and some birds. The most widely known species of the genus is H. pylori which infects up to 50% of the human population. Some strains of this bacterium are pathogenic to humans as it is strongly associated with peptic ulcers, chronic gastritis, duodenitis, and stomach cancer. It also serves as the type species of the genus.

Key Points

- The Epsilonproteobacteria consist of few known genera, mainly the curved to spirilloid Wolinella spp., Helicobacter spp., and Campylobacter spp.

- Most of the known species inhabit the digestive tract of animals and serve as symbionts (Wolinella spp. in cows) or pathogens (Helicobacter spp. in the stomach, Campylobacter spp. in the duodenum).
- There have also been numerous environmental sequences of Epsilonproteobacteria recovered from hydrothermal vents and cold seep habitats.

Key Terms

- **Gram-negative**: Gram-negative bacteria are bacteria that do not retain crystal violet dye in the Gram staining protocol. In a Gram stain test, a counterstain (commonly safranin) is added after the crystal violet, coloring all Gram-negative bacteria with a red or pink color.
- **symbionts**: Symbiosis is close and often long-term interaction between two or more different biological species.
- **Epsilonproteobacteria**: Epsilonproteobacteria is a class of Proteobacteria. All species of this class are, like all Proteobacteria, gram-negative.

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SECTION OVERVIEW

8.8: Gram-Positive Bacteria and Actinobacteria

Topic hierarchy

8.8D: Actinobacteria (High G + C Gram-Positive Bacteria)

8.8A: Overview of Gram-Positive Bacteria and Actinobacteria

8.8B: Non-Spore-Forming Firmicutes

8.8C: Firmicutes

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8.8D: Actinobacteria (High G + C Gram-Positive Bacteria)

Actinobacteria are a group of Gram-positive bacteria with high guanine and cytosine content in their DNA.

Learning Objectives

- Outline the characteristics associated with Actinobacteria

Key Points

- Actinobacteria is one of the dominant phyla of the bacteria.
- Actinobacteria include some of the most common soil life, freshwater life, and marine life, playing an important role in decomposition of organic materials, such as cellulose and chitin, and thereby playing a vital part in organic matter turnover and carbon cycle.
- Actinobacteria are well known as secondary metabolite producers and hence of high pharmacological and commercial interest.
- Some types of Actinobacteria are responsible for the peculiar odor emanating from the soil after rain (Petrichor), mainly in warmer climates.

Key Terms

- **actinobacteria**: A group of Gram-positive bacteria with high guanine and cytosine content in their DNA
- **petrichor**: The distinctive scent which accompanies the first rain after a long warm dry spell.
- **actinomycin**: Any of a class of toxic polypeptide antibiotics found in soil bacteria of genus Streptomyces.

Actinobacteria are a group of Gram-positive bacteria with high guanine and cytosine content in their DNA. They can be terrestrial or aquatic. Actinobacteria is one of the dominant phyla of the bacteria. Analysis of glutamine synthetase sequence has been suggested for phylogenetic analysis of Actinobacteria.

Actinobacteria include some of the most common soil life, freshwater life, and marine life, playing an important role in decomposition of organic materials, such as cellulose and chitin, and thereby playing a vital part in organic matter turnover and carbon cycle. This replenishes the supply of nutrients in the soil and is an important part of humus formation. Other Actinobacteria inhabit plants and animals, including a few pathogens, such as Mycobacterium, Corynebacterium, Nocardia, Rhodococcus, and a few species of Streptomyces.

Actinobacteria are well known as secondary metabolite producers and hence of high pharmacological and commercial interest. In 1940 Selman Waksman discovered that the soil bacteria he was studying made actinomycin, a discovery for which he received a Nobel Prize. Since then, hundreds of naturally occurring antibiotics have been discovered in these terrestrial microorganisms, especially from the genus Streptomyces.

Some Actinobacteria form branching filaments, which somewhat resemble the mycelia of the unrelated fungi, among which they were originally classified under the older name Actinomycetes. Most members are aerobic, but a few, such as Actinomyces israelii, can grow under anaerobic conditions. Unlike the Firmicutes, the other main group of Gram-positive bacteria, they have DNA with a high GC-content, and some Actinomycetes species produce external spores. Some types of Actinobacteria are responsible for the peculiar odor emanating from the soil after rain (Petrichor), mainly in warmer climates. The chemical that produces this odour is known as Geosmin. Most Actinobacteria of medical or economic significance are in subclass Actinobacteridae, order Actinomycetales. While many of these cause disease in humans, Streptomyces is notable as a source of antibiotics. Of those Actinobacteria not in Actinomycetales, Gardnerella is one of the most researched. Classification of Gardnerella is controversial, and MeSH catalogues it as both a gram-positive and gram-negative organism.

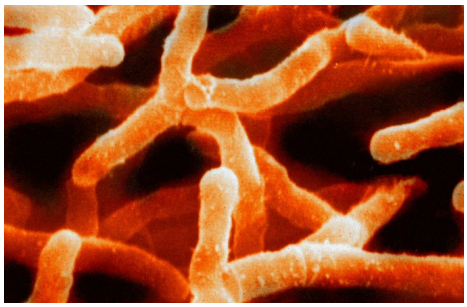

Figure: **Actinomyces israelii**: Scanning electron micrograph of Actinomyces israelii.

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8.8A: Overview of Gram-Positive Bacteria and Actinobacteria

Actinobacteria are Gram-positive bacteria with high guanine and cytosine content in their DNA and can be terrestrial or aquatic.

Learning Objectives

- Discuss the characteristics associated with Actinobacteria

Key Points

- *Actinobacteria* include some of the most common soil life, freshwater life, and marine life, playing an important role in the decomposition of organic materials, such as cellulose and chitin, and thereby playing a vital part in organic matter turnover and carbon cycle.
- *Actinobacteria* are well-known as secondary metabolite producers and are hence of high pharmacological and commercial interest, since they can produce antibiotics like actinomycin.
- *Actinobacteria* are responsible for the peculiar odor emanating from the soil after rain (petrichor), mainly in warmer climates.

Key Terms

- **actinomycin**: Any of a class of toxic polypeptide antibiotics found in soil bacteria of genus Streptomyces.
- **actinobacteria**: A group of Gram-positive bacteria with high guanine and cytosine content in their DNA

Actinobacteria is one of the dominant phyla of bacteria. They are Gram-positive bacteria with high guanine and cytosine content in their DNA and can be terrestrial or aquatic. Analysis of glutamine synthetase sequence has been suggested for their phylogenetic analysis.

Actinobacteria include some of the most common soil life, freshwater life, and marine life, playing an important role in the decomposition of organic materials, such as cellulose and chitin; thereby playing a vital part in organic matter turnover and carbon cycle. This replenishes the supply of nutrients in the soil and is an important part of humus formation.

Other Actinobacteria inhabit plants and animals, including a few pathogens, such as Mycobacterium, Corynebacterium, Nocardia, Rhodococcus, and a few species of Streptomyces.

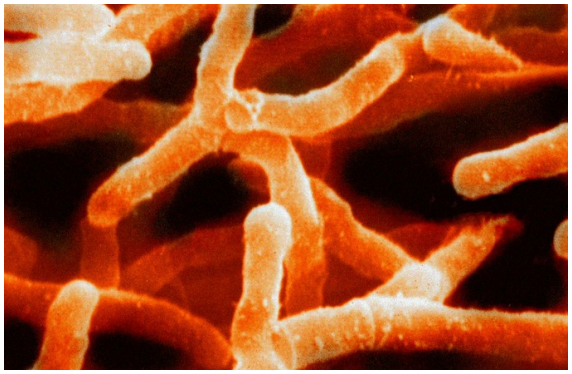

Figure: **Actinomyces israelii**: Scanning electron micrograph of Actinomyces israelii.

Actinobacteria are well-known as secondary metabolite producers and are hence of high pharmacological and commercial interest. In 1940 Selman Waksman discovered that the soil bacteria he was studying made *actinomycin*, a discovery for which he received a Nobel Prize. Since then, hundreds of naturally-occurring antibiotics have been discovered in these terrestrial microorganisms, especially from the genus *Streptomyces*.

Some Actinobacteria form branching filaments, which somewhat resemble the mycelia of the unrelated fungi, among which they were originally classified under the older name *Actinomycetes*. Most members are aerobic, but a few, such as *Actinomyces israelii*, can grow under anaerobic conditions. Unlike the Firmicutes, the other main group of Gram-positive bacteria, they have DNA with a high GC-content, and some Actinomycetes species produce external spores.

Some types of Actinobacteria are responsible for the peculiar odor emanating from the soil after rain (petrichor), mainly in warmer climates. The chemical that produces this odor is known as *Geosmin*. Most Actinobacteria of medical or economic significance are

in subclass *Actinobacteridae*, order *Actinomycetales*. While many of these cause disease in humans, Streptomyces is notable as a source of antibiotics.

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8.8B: Non-Spore-Forming Firmicutes

The *Firmicutes* are a phylum of bacteria, most of which have Gram-positive cell wall structure and some of which do not produce spores.

Learning Objectives

- Discuss the role of non-spore forming Firmicutes in industrial applications, specifically lactic acid bacteria (LAB)

Key Points

- Many Firmicutes produce endospores, which are resistant to desiccation and can survive extreme conditions.
- The lactic acid bacteria (LAB) comprise a class of Firmicutes that are Gram-positive, low-GC, acid-tolerant, generally non-sporulating, and non-respiring.
- The lactic acid bacteria (LAB) are rod-shaped bacilli or cocci characterized by an increased tolerance to a lower pH range.
- LAB are amongst the most important groups of microorganisms used in the food industry and are the most common microbes employed as probiotics.

Key Terms

- **endospore**: A dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.
- **probiotic**: Describing any dietary supplement that contains live bacteria for therapeutic purposes.
- **organoleptic**: Of or pertaining to the sensory properties of a particular food or chemical: its taste, color, odor and feel.

Firmicutes

From Latin: *firmus*, strong; *cutis*, skin; referring to the cell wall. These are a phylum of bacteria, most of which have Gram-positive cell wall structure. A few, however, such as Megasphaera, Pectinatus, Selenomonas and Zymophilus, have a porous pseudo-outer-membrane that causes them to stain Gram-negative.

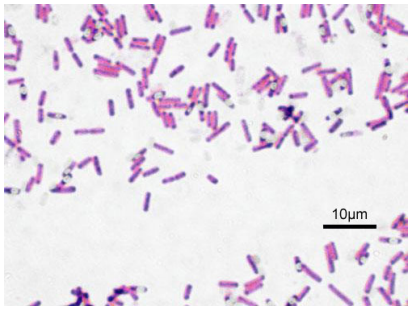

Figure: **Humans use of prokaryotes**: This is a microscopic image of Bacillus subtilis (ATCC 6633) with a gram staining of magnification: 1,000. The oval, unstained structures are spores.

Scientists once classified the Firmicutes to include all Gram-positive bacteria, but have recently defined them to be of a core group of related forms called the low-G+C group, in contrast to the Actinobacteria.

They have round cells, called cocci (singular, coccus), or rod-like forms (bacillus). Many Firmicutes produce endospores, which are resistant to desiccation and can survive extreme conditions. They are found in various environments, and the group includes some notable pathogens. Those in one family, the heliobacteria, produce energy through photosynthesis. Firmicutes play an important role in beer, wine, and cider spoilage.The group is typically divided into the *Clostridia*, which are anaerobic, the *Bacilli*, which are obligate or facultative aerobes, and the *Mollicutes*.

LACTIC ACID BACTERIA (LAB)

These comprise a class of Firmicutes and are Gram-positive, low-GC, acid-tolerant, generally non-sporulating, non-respiring rod or cocci that are associated by their common metabolic and physiological characteristics.

These bacteria, usually found in decomposing plants and lactic products, produce lactic acid as the major metabolic end-product of carbohydrate fermentation. This trait has, throughout history, linked LAB with food fermentations as acidification inhibits the

growth of spoilage agents. Proteinaceous bacteriocins are produced by several LAB strains and provide an additional hurdle for spoilage and pathogenic microorganisms.

Furthermore, lactic acid and other metabolic products contribute to the organoleptic and textural profile of a food item. The industrial importance of the LAB is further evinced by their generally recognized as safe (GRAS) status, due to their ubiquitous appearance in food and their contribution to the healthy microflora of human mucosal surfaces, particularly the gastrointestinal tract.

The lactic acid bacteria (LAB) are rod-shaped bacilli or cocci, characterized by an increased tolerance to a lower pH range. This aspect partially enables LAB to outcompete other bacteria in natural fermentation, as they can withstand the increased acidity from organic acid production (e.g., lactic acid).

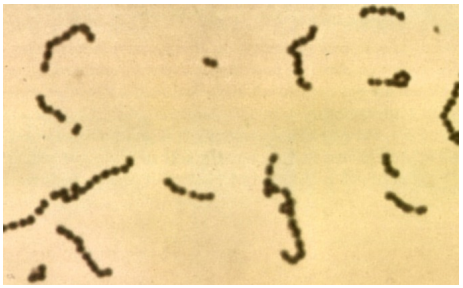

Figure: **Streptococci**: Light microscopy view of streptococci, a non-sporulating lactic acid bacteria.

LAB PATHWAYS

LAB are amongst the most important groups of microorganisms used in the food industry. Two main hexose fermentation pathways are used to classify LAB genera. Under conditions of excess glucose and limited oxygen, homolactic LAB catabolize one mole of glucose in the Embden-Meyerhof-Parnas pathway to yield two moles of pyruvate. Intracellular redox balance is maintained through the oxidation of NADH, concomitant with pyruvate reduction to lactic acid. This process yields two moles of ATP per mole of glucose consumed.

Representative homolactic LAB genera include Lactococcus, Enterococcus and Streptococcus. Heterofermentative LAB in turn use the pentose phosphate pathway, alternatively referred to as the pentose phosphoketolase pathway. One mole of glucose-6-phosphate is initially dehydrogenated to 6-phosphogluconate and subsequently decarboxylated to yield one mole of CO_2. The resulting pentose-5-phosphate is cleaved into one mole glyceraldehyde phosphate (GAP) and one mole acetyl phosphate. GAP is further metabolized to lactate as in homofermentation, with the acetyl phosphate reduced to ethanol via acetyl-CoA and acetaldehyde intermediates.

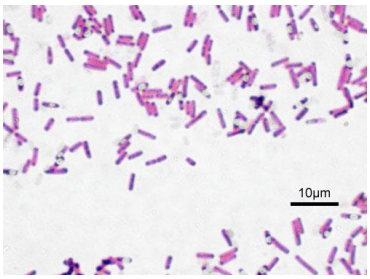

Figure: **Gram staining of Bacillus Subtilis**: A Gram-positive, catalase-positive bacterium which is rod-shaped, and has the ability to form a tough, protective endospore, allowing the organism to tolerate extreme environmental conditions.

In theory, end-products (including ATP) are produced in equimolar quantities from the catabolism of one mole of glucose. Obligate heterofermentative LAB include Leuconostoc, Oenococcus and Weissella.

PROBIOTICS

Strains of LAB are the most common microbes employed as probiotics. Most strains belong to the genus Lactobacillus.

Probiotics have been evaluated in research studies in animals and humans with respect to antibiotic-associated diarrhea, travelers' diarrhea, pediatric diarrhea, inflammatory bowel disease, and irritable bowel syndrome (IBS).

In the future, probiotics will possibly be used for different gastrointestinal diseases, vaginosis, or as delivery systems for vaccines, immunoglobulins, and other therapies.

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8.8C: Firmicutes

Learning Objectives

- Describe the characteristics associated with endospores found in Firmicutes

The *Firmicutes* (Latin: *firmus* = strong, and *cutis* = skin, referring to the cell wall) are a phylum of bacteria, most of which have Gram-positive cell wall structure. A few, however, such as Megasphaera, Pectinatus, Selenomonas and Zymophilus, have a porous pseudo-outer- membrane that causes them to stain Gram-negative. Scientists once classified the Firmicutes to include all Gram-positive bacteria, but have recently defined them to be of a core group of related forms called the low-G+C group, in contrast to the Actinobacteria. They have round cells, called cocci (singular coccus), or rod-like forms (bacillus).

ENDOSPORES

Many Firmicutes produce endospores, which are resistant to desiccation and can survive extreme conditions. They are found in various environments, and the group includes some notable pathogens. Those in one family, the *heliobacteria*, produce energy through photosynthesis. Firmicutes play an important role in beer, wine, and cider spoilage. The group is typically divided into the *Clostridia*, which are anaerobic, the *Bacilli*, which are obligate or facultative aerobes, and the *Mollicutes*. On phylogenetic trees, the first two groups show up as paraphyletic or polyphyletic, as do their main genera, Clostridium and Bacillus.

An endospore is a dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum. The name “endospore” is suggestive of a spore or seed-like form (*endo* means within), but it is not a true spore (i.e. not an offspring). It is a stripped-down, dormant form to which the bacterium can reduce itself.

ENDOSPORE FORMATION

This is usually triggered by a lack of nutrients, and normally occurs in Gram-positive bacteria. It occurs when the bacterium divides within its cell wall. One side then engulfs the other. Endospores enable bacteria to lie dormant for extended periods, even centuries. When the environment becomes more favorable, it can reactivate itself to the vegetative state.

The endospore consists of the bacterium’s DNA and part of its cytoplasm, surrounded by a very tough outer coating. They can survive without nutrients and are resistant to ultraviolet radiation, desiccation, high temperature, extreme freezing and chemical disinfectants. They are commonly found in soil and water, where they may survive for long periods of time. Bacteria produce a single endospore internally.

The spore is sometimes surrounded by a thin covering known as the *exosporium*, which overlies the spore coat, which acts like a sieve that excludes large toxic molecules like *lysozyme*, is resistant to many toxic molecules and may also contain enzymes that are involved in germination. The cortex lies beneath the spore coat and consists of peptidoglycan.

The core wall lies beneath the cortex and surrounds the protoplast or core of the endospore. The core contains the spore chromosomal DNA which is encased in chromatin-like proteins known as SASPs (small acid-soluble spore proteins), that protect the spore DNA from UV radiation and heat. The core also contains normal cell structures, such as ribosomes and other enzymes, but is not metabolically active. Up to 20% of the dry weight of the endospore consists of calcium dipicolinate within the core, which is thought to stabilize the DNA. Dipicolinic acid could be responsible for the heat-resistance of the spore, and calcium may aid in resistance to heat and oxidizing agents.

ENDOSPORE POSITIONING

The position of the endospore differs among bacterial species and is useful in identification. The main types within the cell are terminal, subterminal, and centrally-placed endospores. Terminal endospores are seen at the poles of cells, whereas central endospores are more or less in the middle. Subterminal endospores are those between these two extremes, usually seen far enough towards the poles but close enough to the center so as not to be considered either terminal or central. Lateral endospores are seen occasionally.

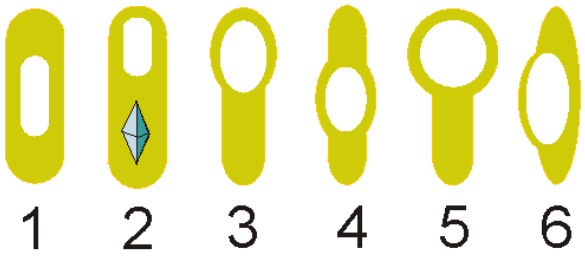

Figure: ***Endospore morphology****: Variations in endospore morphology: (1, 4) central endospore; (2, 3, 5) terminal endospore; (6) lateral endospore.*

When a bacterium detects environmental conditions are becoming unfavorable it may start the process of endosporulation, which takes about eight hours. The DNA is replicated and a membrane wall, known as a spore septum, begins to form between it and the rest of the cell. The plasma membrane of the cell surrounds this wall and pinches off to leave a double membrane around the DNA, and the developing structure is now known as a forespore. Calcium dipicolinate is incorporated into the forespore during this time.

Next the peptidoglycan cortex forms between the two layers and the bacterium adds a spore coat to the outside of the forespore. Sporulation is now complete, and the mature endospore will be released when the surrounding vegetative cell is degraded.

Key Points

- Firmicutes produce endospores, which are resistant to desiccation and can survive extreme conditions.
- An endospore is a dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.
- The endospore consists of the bacterium's DNA and part of its cytoplasm, surrounded by a very tough outer coating.
- Endospores can survive without nutrients and they are resistant to ultraviolet radiation, desiccation, high temperature, extreme freezing and chemical disinfectants.

Key Terms

- **firmicutes**: A phylum of bacteria, most of which have Gram-positive cell wall structure.
- **endospore**: A dormant, tough, and non-reproductive structure produced by certain bacteria from the Firmicute phylum.

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SECTION OVERVIEW

8.9: Nonproteobacteria Gram-Negative Bacteria

Topic hierarchy

8.9A: Cyanobacteria

8.9B: Anoxygenic Photosynthetic Bacteria

8.9C: Prochlorophytes

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8.9A: Cyanobacteria

Learning Objectives

Describe the characteristics associated with Cyanobacteria including: cell types, forms of motility and metabolic properties

- Explain the following laws within the Ideal Gas Law

Cyanobacteria, also known as blue-green bacteria, blue-green algae, and Cyanophyta, is a phylum of bacteria that obtain their energy through photosynthesis. The ability of cyanobacteria to perform oxygenic photosynthesis is thought to have converted the early reducing atmosphere into an oxidizing one, which dramatically changed the composition of life forms on Earth by stimulating biodiversity and leading to the near-extinction of oxygen-intolerant organisms. According to the endosymbiotic theory, chloroplasts in plants and eukaryotic algae have evolved from cyanobacterial ancestors via endosymbiosis.

DISTRIBUTION AND EFFECT ON ECOSYSTEMS

Cyanobacteria can be found in almost every terrestrial and aquatic habitat. Aquatic cyanobacteria are probably best known for the extensive and visible blooms that can form in both freshwater and the marine environment. These can have the appearance of blue-green paint or scum. The association of toxicity with such blooms has frequently led to the closure of recreational waters when blooms are observed. Cyanobacteria include unicellular and colonial species. Colonies may form filaments, sheets, or even hollow balls. Some filamentous colonies show the ability to differentiate into several different cell types, including:

- Vegetative cells, the normal, photosynthetic cells that are formed under favorable growing conditions.
- Akinetes, the climate-resistant spores that may form when environmental conditions become harsh.
- Thick-walled heterocysts, which contain the enzyme nitrogenase, vital for nitrogen fixation. Heterocysts may also form under the appropriate environmental conditions (anoxic) when fixed nitrogen is scarce.

Heterocyst-forming species are specialized for nitrogen fixation and are able to bind nitrogen gas to ammonia (NH_3), nitrites (NO^{-}_2) or nitrates (NO^{-}_3). These molecules can be absorbed by plants and converted into protein and nucleic acids.

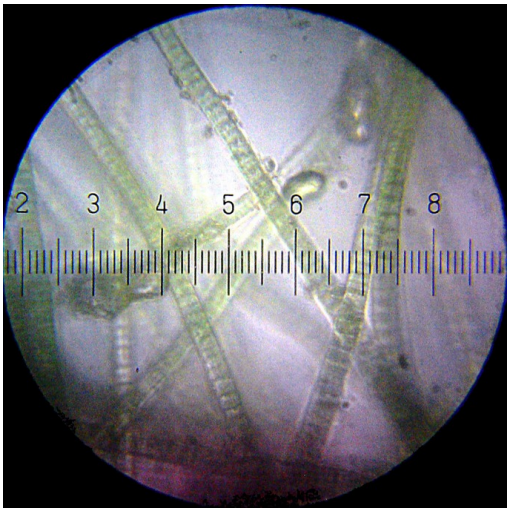

Figure: Cyanobacteria: Cyanobacteria, also known as blue-green bacteria, blue-green algae, and Cyanophyta, is a phylum of bacteria that obtain their energy through photosynthesis

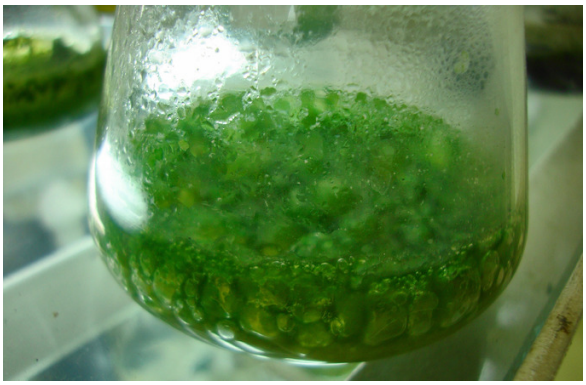

Figure: Blue-green algae cultured in specific media: Cyanobacteria cultured in specific media. Cyanobacteria can be helpful in agriculture as they have the capability to fix atmospheric nitrogen to soil.

Hormogonia

Many cyanobacteria form motile filaments called hormogonia, that travel from the main biomass to bud and form new colonies elsewhere. The cells in a hormogonium are often thinner than those found in the vegetative state, and the cells on either end of the motile chain may be tapered. To break away from the parent colony, a hormogonium often must tear a weaker filament cell, called a necridium.

CYANOBACTERIUM CELLS AND MOTILITY

Individual cells of a cyanobacterium typically have a thick, gelatinous cell wall. They lack flagella, but hormogonia and some species may move about by gliding along surfaces. Many of the multi-cellular filamentous forms of Oscillatoria are capable of a waving motion; the filament oscillates back and forth. In water columns some cyanobacteria float by forming gas vesicles, like in archaea. These vesicles are not organelles as such. They are not bounded by lipid membranes but by a protein sheath.

PHOTOSYNTHESIS AND OTHER METABOLIC PROCESSES

Cyanobacteria use the energy of sunlight to drive photosynthesis, a process where the energy of light is used to split water molecules into oxygen, protons, and electrons. As with any prokaryotic organism, cyanobacter does not show nuclei nor internal membranes; many cyanobacter species have folds on their external membranes which function in photosynthesis. Cyanobacteria get their color from the bluish pigment phycocyanin, which they use to capture light for photosynthesis.

Photosynthesis in cyanobacteria generally uses water as an electron donor and produces oxygen as a by-product, though some species may also use hydrogen sulfide as occurs among other photosynthetic bacteria. Carbon dioxide is reduced to form carbohydrates via the Calvin cycle. In most forms the photosynthetic machinery is embedded into folds of the cell membrane, called thylakoids.

Because of their ability to fix nitrogen in aerobic conditions they are often found in symbiontic partnerships with a number of other groups of organisms, including but not limited to fungi (lichens), corals, pteridophytes (Azolla), and angiosperms (Gunnera).

Many cyanobacteria are able to reduce ambient levels of nitrogen and carbon dioxide under aerobic conditions, a fact that may be responsible for their evolutionary and ecological success. The water-oxidizing photosynthesis is accomplished by coupling the activity of photosystem (PS) II and I (Z-scheme). In anaerobic conditions, they are also able to use only PS I—cyclic photophosphorylation—with electron donors other than water (for example hydrogen sulfide), in the same way as the purple photosynthetic bacteria.

They also share an archaeal property, the ability to reduce elemental sulfur by anaerobic respiration in the dark. Their photosynthetic electron transport shares the same compartment as the components of respiratory electron transport. Their plasma membrane contains only components of the respiratory chain, while the thylakoid membrane hosts both respiratory and photosynthetic electron transport.

Classification

The cyanobacteria were traditionally classified by morphology into five sections, referred to by the numerals I-V. The first three–Chroococcales, Pleurocapsales, and Oscillatoriales–are not supported by phylogenetic studies. However, the latter two–Nostocales

and Stigonematales–are monophyletic, and make up the heterocystous cyanobacteria. Some cyanobacteria produce toxins, called cyanotoxins. This results in algal blooms, which can become harmful to other species including humans if the cyanobacteria involved produce toxins.

Key Points

- Cyanobacteria can be found in almost every terrestrial and aquatic habitat.
- Cyanobacteria include unicellular and colonial species.
- Cyanobacteria use the energy of sunlight to drive photosynthesis, a process where the energy of light is used to split water molecules into oxygen, protons, and electrons.
- Many cyanobacteria are able to reduce nitrogen and carbon dioxide under aerobic conditions, which may be responsible for their evolutionary and ecological success.

Key Terms

- cyanobacteria: Cyanobacteria, also known as blue-green bacteria, blue-green algae, and Cyanophyta, is a phylum of bacteria that obtain their energy through photosynthesis.
- photosynthesis: The process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts.
- heterocyst: A specialized nitrogen-fixing cell formed by some filamentous cyanobacteria.

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8.9B: Anoxygenic Photosynthetic Bacteria

Learning Objectives

- Describe the mechanisms that specific bacteria use to undergo anoxygenic photosynthetic bacteria, including: green sulfur and purple sulfur bacteria

Phototrophy is the process by which organisms trap light energy (photons) and store it as chemical energy in the form of ATP and/or reducing power in NADPH. There are two major types of phototrophy: chlorophyll-based chlorophototrophy and rhodopsin-based retinalophototrophy. Chlorophototrophy can further be divided into oxygenic photosynthesis and anoxygenic phototrophy.

Oxygenic and anoxygenic photosynthesizing organisms undergo different reactions, either in the presence of light or with no direct contribution of light to the chemical reaction (colloquially called “light reactions” and “dark reactions”, respectively). Anoxygenic photosynthesis is the phototrophic process where light energy is captured and converted to ATP, without the production of oxygen; water is, therefore, not used as an electron donor. There are several groups of bacteria that undergo anoxygenic photosynthesis: green sulfur bacteria, green and red filamentous anoxygenic phototrophs (FAPs), phototrophic purple bacteria, phototrophic acidobacteria, and phototrophic heliobacteria.

ANOXYGENIC PHOTOTROPHS

Anoxygenic phototrophs have photosynthetic pigments called bacteriochlorophylls; these are similar to chlorophyll found in eukaryotes. Bacteriochlorophyll a and b have wavelengths of maximum absorption at 775 nm and 790 nm, respectively. Unlike oxygenic phototrophs, anoxygenic photosynthesis only functions using either one of two possible types of photosystem. This restricts them to cyclic electron flow; they are therefore unable to produce O2 from the oxidization of H2O.

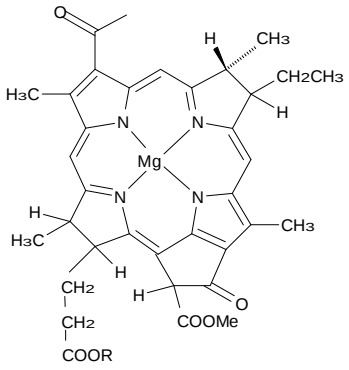

Figure: Bacteriochlorophyll a: Bacteriochlorophylls are photosynthetic pigments that occur in various phototrophic bacteria. They are related to chlorophylls, which are the primary pigments in plants, algae, and cyanobacteria.

GREEN SULFUR BACTERIA

The green sulfur bacteria are a family of obligately anaerobic photoautotrophic bacteria most closely related to the distant Bacteroidetes. They are non-motile with the exception of Chloroherpeton thalassium, which may glide. They come in sphere, rods, and spiral forms. Photosynthesis is achieved using bacteriochlorophyll (BChl) c, d, or e, in addition to BChl a and chlorophyll a, in chlorosomes attached to the membrane. The electron transport chain (ETC) of green sulfur bacteria uses the reaction centre bacteriochlorophyll pair, P840. When light is absorbed by the reaction center, P840 enters an excited state with a large negative reduction potential, and so readily donates the electron to bacteriochlorophyll 663 which passes it on down the electron chain. The electron is transferred through a series of electron carriers and complexes until it either returns to P840 or is used to reduce NAD+. If the electron leaves the chain to reduce NAD+, P840 must be reduced for the ETC to function again. The green sulfur bacterias’ small dependence on organic molecule transporters and transcription factors indicates that these organisms are adapted to a narrow range of energy-limited conditions, and fit into an ecology shared with the simpler cyanobacteria,



Figure: *Green d winogradsky: A column containing green sulfur bacteria which uses anoxygenic photosynthesis.*

PURPLE SULFUR BACTERIA

The purple sulfur bacteria are a group of Proteobacteria capable of photosynthesis. They are anaerobic or microaerophilic, and are often found in hot springs or stagnant water. Unlike plants, algae, and cyanobacteria, they do not use water as their reducing agent, and so do not produce oxygen. Instead, they use hydrogen sulfide, which is oxidized to produce granules of elemental sulfur. This in turn may be oxidized to form sulfuric acid.The purple sulfur bacteria are divided into two families: the Chromatiaceae and Ectothiorhodospiraceae, which respectively produce internal and external sulfur granules, and show differences in the structure of their internal membranes.

Purple sulfur bacteria are generally found in illuminated anoxic zones of lakes and other aquatic habitats where hydrogen sulfide accumulates. They are also found in “sulfur springs” where geochemically or biologically produced hydrogen sulfide can trigger the formation of blooms of purple sulfur bacteria. Anoxic conditions are required for photosynthesis; these bacteria cannot thrive in oxygenated environments. The electron transport chain of purple non-sulfur bacteria begins when the reaction center bacteriochlorophyll pair, P870, becomes excited by the absorption of light. Excited P870 will then donate an electron to Bacteriopheophytin, which then passes it on to a series of electron carriers down the electron chain. In the process, it will generate a proton motor force (PMF) which can then be used to synthesize ATP by oxidative phosphorylation. The electron returns to P870 at the end of the chain so it can be used again once light excites the reaction-center.

Key Points

- There are several groups of bacteria that undergo anoxygenic photosynthesis: green sulfur bacteria, green and red filamentous anoxygenic phototrophs (FAPs), phototrophic purple bacteria, phototrophic acidobacteria, and phototrophic heliobacteria.
- Anoxygenic phototrophs have photosynthetic pigments called bacteriochlorophylls similar to chlorophyll found in eukaryotes.
- Green sulfur bacteria are a family of obligately anaerobic photoautotrophic bacteria most closely related to the distant Bacteroidetes which are adapted to a narrow range of energy-limited conditions, an ecology shared with the simpler cyanobacteria.
- Purple sulfur bacteria are a group of Proteobacteria capable of photosynthesis, anaerobic or microaerophilic, and often found in hot springs or stagnant water.

Key Terms

- anoxygenic: That does not involve the production of oxygen
- photosynthesis: The process by which plants and other photoautotrophs generate carbohydrates and oxygen from carbon dioxide, water, and light energy in chloroplasts.
- photoautotroph: An organism, such as all green plants, that can synthesize its own food from inorganic material using light as a source of energy

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8.9C: Prochlorophytes

Learning Objectives

- Describe the characteristics associated with Prochlorophytes, a member of the Picoplankton

Picoplankton is the fraction of plankton, composed by cells between 0.2 and 2 µm, that is either photosynthetic (photosynthetic picoplankton;) or heterotrophic (heterotrophic picoplankton). Some species are also mixotrophic. Picoplankton are responsible for the majority of the primary productivity in oligotrophic gyres, and are different from nanoplankton and microplankton. Because they are small, they have a greater surface-to-volume ratio, which enables them to obtain scarce nutrients in these ecosystems.

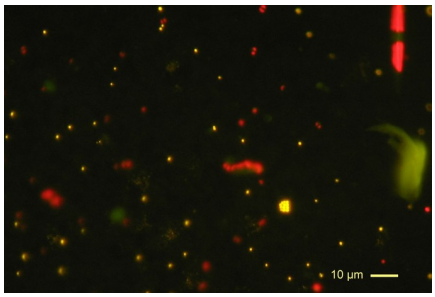

Figure: *Prokaryotes vs. Eukaryotes: Picoplankton observed by epifluorescence microscopy, a technique which allows the detection of certain groups of cells possessing fluorescent pigments; and example would be Synechococcus, which possess phycoerythrin*

Prochlorophyta are a photosynthetic prokaryote member of the phytoplankton group Picoplankton. These oligotrophic organisms are abundant in nutrient-poor tropical waters and use a unique photosynthetic pigment, divinyl-chlorophyll, to absorb light and acquire energy. These organisms lack red and blue Phycobilin pigments and have staked thylakoids, both of which make them different from Cyanophyta (Cyanobacteria). Prochlorophyta were initially discovered in 1975 near the Great Barrier Reef and off the coast of Mexico. The following year, Ralph A. Lewin, of the Scripps Institution of Oceanography, assigned them as a new algal sub-class.

In addition to Prochlorophyta, other phytoplankton that lack Phycobilin pigments were later found in freshwater lakes in the Netherlands, by Tineke Burger-Wiersma. These organisms were termed Prochlorothrix. In 1986, Prochlorococcus was discovered by Sallie W. Chisholm and his colleagues. These organisms might be responsible for a significant portion of the global primary production.

Prochlorophytes are very small microbes generally between 0.2 and 2 µm (Photosynthetic picoplankton). They morphologically resemble Cyanobacteria, formally known as Blue Green Algae. Members of Prochlorophyta have been found as coccoid (spherical) shapes, like Prochlorococcus, and as filaments, like Prochlorothrix.

Key Points

- Picoplankton are responsible for the majority of the primary productivity in oligotrophic gyres, and are different from nanoplankton and microplankton.
- Because they are small, they have a greater surface-to-volume ratio. This enables them to obtain the scarce nutrients in these ecosystems.
- Prochlorophyta are a photosynthetic prokaryote member of the phytoplankton group Picoplankton. They are abundant in nutrient poor tropical waters and use a unique photosynthetic pigment, divinyl-chlorophyll, to absorb light and acquire energy.

Key Terms

- prochlorophyta: a photosynthetic prokaryote member of the phytoplankton group Picoplankton
- picoplankton: plankton composed of cells between 0.2 and 2 micrometers that are either photosynthetic or heterotrophic

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SECTION OVERVIEW

8.10: Irregular Bacterial cells

Topic hierarchy

8.10A: Chlamydiae

8.10B: Planctomycetes

8.10C: Verrucomicrobia

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8.10A: Chlamydiae

Chlamydiae are a bacterial phylum and class whose members are obligate intracellular pathogens.

Learning Objectives

- Discuss the evidence that supports Chlamydiae as a unique bacterial evolutionary group

Key Points

- Chlamydiae replicate inside the host cells and are termed intracellular.
- Most intracellular chlamydiae are located in an inclusion body or vacuole.
- Chlamydiae is a unique bacterial evolutionary group that separated from other bacteria approximately a billion years ago. It falls into the clade Planctobacteria in the larger clade Gracilicutes.
- Chlamydia infection is a common sexually transmitted infection (STI) in humans caused by the bacterium Chlamydia trachomatis.

Key Terms

- **chlamydiae**: Chlamydiae is a bacterial phylum and class whose members are obligate intracellular pathogens.
- **inclusion body**: Inclusion bodies are nuclear or cytoplasmic aggregates of stainable substances, usually proteins.

Chlamydiae are a bacterial phylum and class whose members are obligate intracellular pathogens. Many chlamydiae coexist in an asymptomatic state within specific hosts. It is widely believed that these hosts provide a natural reservoir for these species. All known chlamydiae only grow by infecting eukaryotic host cells. They are as small or smaller than many viruses.

Chlamydiae replicate inside the host cells and are termed intracellular. Most intracellular chlamydiae are located in an inclusion body or vacuole. Outside of cells they survive only as an extracellular infectious form. Chlamydiae can only grow where their host cells grow. Therefore, chlamydiae cannot be propagated in bacterial culture media in the clinical laboratory. Chlamydiae are most successfully isolated while still inside their host cell.

Chlamydiae is a unique bacterial evolutionary group that separated from other bacteria approximately a billion years ago. Cavalier-Smith has postulated that the Chlamydiae fall into the clade Planctobacteria in the larger clade Gracilicutes. The species from this group can be distinguished from all other bacteria by the presence of conserved indels in a number of proteins such as RNA polymerase alpha subunit, Gyrase B, Elongation factor-Tu and Elongation factor-P, and by large numbers of signature proteins that are uniquely present in different chlamydiae species. Reports have varied as to whether Chlamydiae is related to Planctomycetales or Spirochaetes. However, genome sequencing indicates that 11% of the genes in Candidatus Protochlamydia amoebophila UWE25 and 4% in Chlamydiaceae are most similar to chloroplast, plant, and cyanobacterial genes. Phylogeny and shared presence of conserved indels in proteins such as RNA polymerase Beta subunit and lysyl-tRNA synthetase indicate that Verrucomicrobia are the closest free-living relatives of these parasitic organisms.

There are three described species of chlamydiae that commonly infect humans:

1. Chlamydia trachomatis, which causes the eye-disease trachoma and the sexually transmitted infection chlamydia.

2. Chlamydia pneumoniae, which causes a form of pneumonia.

3. Chlamydia psittaci, which causes psittacosis.

Chlamydia infection is a common sexually transmitted infection (STI) in humans caused by the bacterium Chlamydia trachomatis. The term Chlamydia infection can also refer to infection caused by any species belonging to the bacterial family Chlamydiaceae. C. trachomatis is found only in humans. Chlamydia is a major cause of blindness today, especially in developing countries.

Risk factors include a history of chlamydial or other sexually transmitted infection, new or multiple sexual partners, and inconsistent condom use. C. trachomatis infection can be effectively cured with antibiotics once it is detected. Current guidelines recommend: azithromycin, doxycycline, erythromycin, or ofloxacin. Agents recommended for pregnant women include erythromycin or amoxicillin.

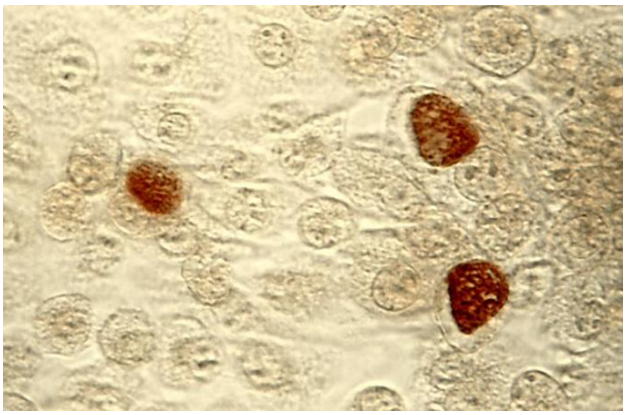

Figure: **Chlamydias bacteria group**: Light microscope view of cells infected with chlamydiae as shown by the brown inclusion bodies.

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8.10B: Planctomycetes

Planctomycetes are a phylum of aquatic bacteria and are found in samples of brackish, marine, and fresh water.

Learning Objectives

- Describe the characteristics associated with Planctomycetes

Key Points

- In structure, the organisms of this group are ovoid and have a holdfast, called the stalk, at the non-reproductive end that helps them to attach to each other during budding.
- The organisms belonging to this group have a glycoprotein rich in glutamate instead of murein in their cell wall.
- The nuclear material in planctomycetes can sometimes be enclosed in a double membrane.

Key Terms

- **nucleoid**: The irregularly-shaped region within a prokaryote cell where the genetic material is localized.
- **operon**: A unit of genetic material that functions in a coordinated manner by means of an operator, a promoter, and structural genes that are transcribed together.
- **planctomycetes**: A phylum of aquatic bacteria that are found in samples of brackish, and marine and fresh water.
- **budding**: a form of asexual reproduction in which a new organism develops from an outgrowth or bud on another one

Planctomycetes are a phylum of aquatic bacteria. They are found in samples of brackish, marine, and fresh water. They reproduce by budding. In structure, the organisms of this group are ovoid and have a holdfast, called the stalk, at the non-reproductive end that helps them to attach to each other during budding.

The organisms belonging to this group lack murein in their cell wall. Murein is an important heteropolymer present in most bacterial cell walls that serves as a protective component in the cell wall skeleton. Instead, their walls are made up of glycoprotein rich in glutamate. Planctomycetes have internal structures that are more complex than typically expected in prokaryotes. While they do not have a nucleus in the eukaryotic sense, the nuclear material can sometimes be enclosed in a double membrane. In addition to this nucleoid, there are two other membrane-separated compartments; the pirellulosome or riboplasm, which contains the ribosome and related proteins, and the ribosome-free paryphoplasm.

Cavalier-Smith has postulated that the Planctomycetes are within the clade Planctobacteria in the larger clade Gracilicutes. RNA sequencing shows that the planctomycetes are related to the Verrucomicrobia and possibly the Chlamydiae. A number of essential pathways are not organized as operons, which is unusual for bacteria. A number of genes have been found (through sequence comparisons) that are similar to genes found in eukaryotes. One such example is a gene sequence (in Gemmata obscuriglobus) that was found to have significant homology to the integrin alpha-V, a protein that is important in transmembrane signal transduction in eukaryotes. The life cycle of many planctomycetes involves alternation between sessile cells and flagellated swarmer cells. The sessile cells bud to form the flagellated swarmer cells which swim for a while before settling down to attach and begin reproduction.

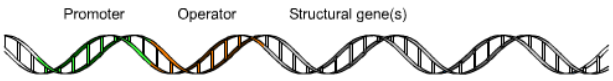

Figure: **Operon**: In genetics, an operon is a functioning unit of genomic DNA containing a cluster of genes under the control of a single regulatory signal or promoter.

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8.10C: Verrucomicrobia

Verrucomicrobia is a recently described phylum of bacteria which is part of the PVC superphylum.

Learning Objectives

- Describe the structure of Verrucomicrobia and its placement in the PVC superphylum

Key Points

- The PVC group includes Chlamydiae, Lentisphaerae, Planctomycetes, Verrucomicrobia, Poribacteria and OP3.
- Verrucomicrobia possess a compartmentalised cell plan with a condensed nucleoid and the ribosomes pirellulosome (enclosed by the intracytoplasmic membrane) and paryphoplasm compartment between the intracytoplasmic membrane and cytoplasmic membrane.
- Evidence suggests that verrucomicrobia are abundant within the environment, and important (especially to soil cultures).

Key Terms

- **verrucomicrobia**: Verrucomicrobia is a recently described phylum of bacteria which is part of the PVC superphylum and they possess a compartmentalised cell plan with a condensed nucleoid.

Verrucomicrobia is a recently described phylum of bacteria which is part of the PVC superphylum. The PVC group includes Chlamydiae, Lentisphaerae, Planctomycetes, Verrucomicrobia, Poribacteria and OP3. Support for this superphylum has been found by examining the RNA polymerase protein RpoB.

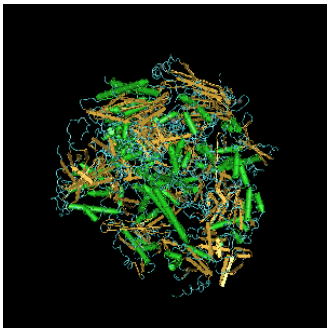

Figure: **RNA polymerase II**: RNA polymerase II (also called RNAP II and Pol II) is an enzyme found in eukaryotic cells. It catalyzes the transcription of DNA to synthesize precursors of mRNA and most snRNA and microRNA.

RpoB is the gene that encodes the β subunit of bacterial RNA polymerase. This protein has a unique 3 amino acid insert in all sequenced Chlamydiae, Lentisphaerae and Verrucomicrobia species. In addition, a conserved protein of unknown function is present in all sequenced species from the phyla Chlamydiae, Lentisphaerae, Planctomycetes and Verrucomicrobia. This protein is absent in the Poribacteria. Study of additional proteins from this proposed superphylum suggests that the Poribacteria may be separate from this clade. The Planctomycetes may be basal to the Chlamydiae-Verrucomicrobia-Lentisphaerae clade.

Like the Planctomycetes species, Verrucomicrobia possess a compartmentalised cell plan with a condensed nucleoid and the ribosomes pirellulosome (enclosed by the intracytoplasmic membrane) and paryphoplasm compartment between the intracytoplasmic membrane and cytoplasmic membrane. Cavalier-Smith has postulated that the Verrucomicrobia belong in the clade Planctobacteria in the larger clade Gracilicutes. 16S rRNA data corroborate that view. In 2008, the whole genome of Methylacidiphilum infernorum (2.3 Mbp) was published. On the single circular chromosome, 2473 predicted proteins were found, 731 of which had no detectable homologs. These analyses also revealed many possible homologs with Proteobacteria.

Evidence suggests that verrucomicrobia are abundant within the environment, and are important especially to soil cultures. Verrucomicrobia have been isolated from fresh water, soil environments and human feces. A number of as-yet uncultivated species have been identified in association with eukaryotic hosts including extrusive explosive ectosymbionts of protists and endosymbionts of nematodes residing in their gametes. While verrucae is another name for the warts often found on the hands and feet, this phylum is so called not because it is a causative agent thereof, but because of its wart-like morphology.

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SECTION OVERVIEW

8.11: Other Bacterial Groups

Topic hierarchy

8.11A: Bacteroides and Flavobacterium

8.11B: Acidobacteria

8.11C: Cytophaga and Relatives

8.11D: Bacteroidetes and Chlorobi

8.11E: Fusobacteria

8.11F: Spirochaetes

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8.11A: Bacteroides and Flavobacterium

Bacteroides and Flavobacterium are both Gram-negative bacteria that can be either motile or non-motile.

Learning Objectives

- Describe the role of Bacteroides in the normal flora of the human gastrointestinal tract and the role of Flavobacterium in causing disease in freshwater fish

Key Points

- Bacteroides are characterized by their mutualistic behavior and are typically present in the gastrointestinal tract of mammals to function as normal flora.
- Bacteroides are capable of breaking down and processing large complex molecules within the intestine.
- Flavobacterium are found in both soil and fresh water environments. Pathogenic strains of Flavobacterium can infect fish such as salmonids and trouts.

Key Terms

- **mutualistic**: Mutually beneficial.
- **normal flora**: The aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. Also known as human microbiota.

Bacteroides include a specific genus of gram-negative bacillus bacteria. This genus of bacteria is characterized by their sphingolipid based membranes and are typically non-endospore forming and anaerobic. The bacteroides are further characterized as mutualistic and have been identified in the mammalian gastrointestinal system. The ability of the bacteroides to function in an anaerobic environment allow them to reside in the abdominal cavity in aerotolerant conditions. The presence of bacteroides in the normal flora of mammals is indicative of its role in processing complex molecules to simpler ones that can be utilized by the host. The energy sources for the bacteroides are typically derived from the host. The role of bacteroides in the normal flora extends beyond their ability to breakdown larger complex molecules and can display protective function. The bacteroides are able to benefit the host by preventing infection by potential pathogens that may colonize and infect the gut as well. Due to the abundancy of the bacteroides within the gastrointestinal system, bacteroides constitute a significant portion of the fecal bacterial population.

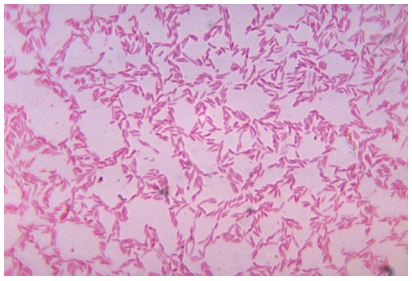

Figure: **Bacteroides biacutus**: An image of Bacteroides biacutus, an anaerobic bacterium present within the gastrointestinal tract.

Flavobacterium include a specific genus of gram-negative bacteria that are characterized by their presence in soil and fresh water environments. Flavobacterium can be either non-motile or motile and are rod-shaped. To date, there are 10 established species of flavobacterium and several new proposed species. The flavbacterium are characterized by their ability to cause disease in freshwater fish such as salmon and rainbow trouts. For example, the species *Flavobacterium psychrophilum* is responsible for causing Bacterial Cold Water Disease (BCWD) on salmonids and Rainbow Trout Fry Disease (RTFS) on rainbow trouts. The species *Flavobacterium branchiophilum* causes the Bacterial Gill Disease (BGD) on trouts.

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8.11B: Acidobacteria

Acidobacteria are a newly formed phylum of bacteria that are physiologically diverse and abundant in soil environments.

Learning Objectives

- Discuss the advantages that Acidobacteria have developed due to their ability to thrive in acidic conditions

Key Points

- Many acidobacteria can be classified as acidophilic organisms because they are able to thrive and reside within highly acidic environments.
- The acidobacteria that are considered to be acidophilic have developed efficient and effective mechanisms to pump out protons to ensure their intracellular environments remains at a neutral pH.
- It is hypothesized that acidobacteria play a major role in the ecosystem based on their abundance in soil.

Key Terms

- **acidophilic**: Being an acidophile.

Members of Acidobacteria are physiologically diverse. They were first recognized as a novel division in 1997. The members of this phylum are acidophilic, physiologically diverse, and are ubiquitous in soils. The Phylum can be further broken down in Class Acidobacteria with Order Acidobacteriales and Class Solibacteres with Order Solibacterales.

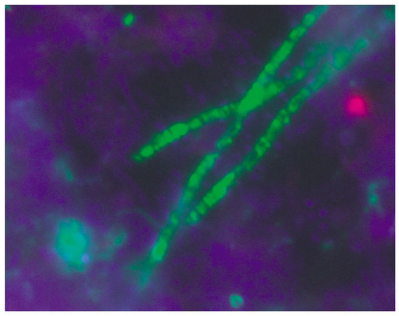

Figure: **Acdiobacterium**: An image of an Acidobacteria.

Acidophilic organisms are capable of thriving under highly acidic conditions. The ability to thrive under acidic conditions has promoted the evolution of highly efficient and effective mechanisms that lend them protection in these environments. For example, most acidophiles are able to pump protons out of the intracellular space to maintain a neutral pH within the cytoplasm. The mechanisms used to pump protons out are quick and effective. This is advantageous as the intracellular proteins are not required to develop tolerance against highly acidic conditions. However, not all members of this phylum are considered to be acidophilic.

Since they have only recently been discovered and the large majority have not been cultured, the ecology and metabolism of these bacteria is not well understood. However, these bacteria may be an important contributor to ecosystems, since they are particularly abundant within soils. The first species of this phylum, Acidobacterium capsulatum, was discovered in 1991. Other notable species are Holophaga foetida, Geothrix fermentans, Acanthopleuribacter pedis, and Bryobacter aggregatus.

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8.11C: Cytophaga and Relatives

Cytophaga are a type of bacteria characterized as Gram-negative, rod shaped bacteria that utilize a gliding mechanism for locomotion.

Learning Objectives

- Describe the unique form of locomotion for Cytophaga

Key Points

- Cytophaga are commonly associated with infections found on fish as a result of abnormal water temperatures that promote growth.
- Cytophaga columnaris is responsible for columnaris disease in salmonid fish in abnormally high water temperatures and result in lesion and ulcerations on the gill.
- Cytophaga psychrophila is responsible for the cold water disease in trout and results in skin lesions and occurs in subnormal water temperatures.

Key Terms

- **myxobacteria**: A type of bacteria known as the “slime bacteria” that reside in soil and feed on insoluble organic matter.
- **columnaris**: A disease characterized by the presence of ulcerations on the skin and the development of fungus-like patches on the gill filaments.

Cytophaga represent gram-negative, gliding, rod-shaped bacteria. The bacterial gliding is a form of locomotion utilized by Cytophaga that allows the bacteria to move under its own power. In this specific type of locomotion, the exact mechanisms are unknown, but it is known that this process does not require a flagella. However, a few mechanisms have been partially identified in certain species that utilize the gliding locomotion and these include the use of a type IV pili, the use of focal adhesion complexes distributed through the body, and the use of a polysaccharide slime that is ejected from one the ends of the body. Gliding can also be found in bacteria that are categorized as cyanobacteria and myxobacteria.



Figure: **Columnaris disease**: An image of a chinook salmon that has been infected with Cytophaga columnaris and has lesions and ulcerations on the gill.

Cytophaga include the following species: *Cytophaga columnaris*, *Cytophaga johnsonae*, and *Cytophaga psychrophila*. The *Cytophaga columnaris*, also referred to as *Flavobacterium columnare* or *Bacillus columnaris*, are responsible for the columnaris disease in salmonid fish. Columnaris disease is characterized by the presence of ulcerations on the skin and the development of fungus-like patches on the gill filaments. This disease is highly contagious and fatal due to the damage of the gills. The *Cytophaga johnsonae*, or *Flavobacterium johnsonae*, are associated with false columnaris disease which is similar to columnaris disease and characterized by the presence of damage at the gills. Lastly, the species *Cytophaga psychrophila*, or*Flavobacterium psychrophilum*, is responsible for causing bacterial cold water disease (BCWD) in salmonid fish. The disease occurs at subnormal water temperatures and results in lesions on the skin and fins. The Cytophaga species are now referred to as Flavobacterium due to further characterization and change in phylogeny.

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8.11D: Bacteroidetes and Chlorobi

Bacteria categorized under the Phylum Bacteroidetes and Phlyum Chlorobi are closely related base on comparative genomic analysis.

Learning Objectives

- Describe the major classes of Bacteroidetes, including: Bacteroidia and Porphyromonas a well as Phlyum Chlorobi

Key Points

- The close relationship between Phylum Bacteroidetes and Phylum Chlorobi are supported by comparative genomic analysis which indicates they are derived from a common ancestor based on unique molecular signatures and common proteins.
- Phylum Bacteroidetes are composed of three large classes of gram-negative bacteria that are rod-shaped, non-spore forming, and present in anaerobic conditions. Bacteroidetes are found in numerous environments ranging from soils, sediments, sea water, and the guts and skin of animals.
- Phylum Chlorobi are composed of green sulfur bacteria that are categorized as photolithotrophic oxidizers of sulfur. Chlorobi species are commonly found in symbiotic relationships with colorless, nonphotosynthetic bacteria.

Key Terms

- **photolithotropic**: Obtain energy from light and use inorganic electron donors only to fuel biosynthetic reactions.



Figure: **Green sulfur bacteria**: An image of a green sulfur bacteria which is categorized under the Phlyum Chlorobi and shares a close relationship with bacteria in the Phlyum Bacteroidetes.

The Phylum Bacteroidetes are characterized as rod-shaped, gram-negative bacteria that are non-spore forming and are present in anaerobic environments. Bacteroidetes are capable of thriving in numerous environments that include soil, sediments, sea water, and in the guts and on skin of animal hosts. The Bacteroidetes are classified into three large classes which include the Bacteroidia class and the Porphyromonas class. The Bacteroidia class is the most studied and is present in the gastrointestinal system of mammals which allows it to be abundant in the feces. The Porphyromonas class is characterized by their presence in the oral cavity of humans. The bacteria categorized as bacteroidetes are opportunistic and are rarely pathogenic as they constitute part of the normal flora.

The Phylum Chlorobi are characterized by bacteria that are obligately anaerobic photoautotrophic which includes green sulfur bacteria. The green sulfur bacteria are photolithotropic oxidizers of sulfur and utilize a noncyclic electron transport chain. The green sulfur bacteria are closely related to Bacteroidetes and are non-motile and can be found as sphere, rod, or spiral shaped. The most commonly studied model is *Chlorobium tepidum* which has had its complete genome sequences. Chlorobium species typically exist in symbiotic relationships with a colorless, nonphotosynthetic bacteria.

The Phlyum Chlorobi is often grouped with the Phlyum Bacteroidetes because their branches are very close together in the phylogenetic tree. By utilizing sequencing techniques such as comparative genomic analysis, there have been three proteins which

are unique to all members of the Bacteroidetes and Chlorobi phyla but not to other bacteria indicating a conserved protein signature. Further analysis has identified additional molecular signatures that support the close relationship between these two phyla as well indicating a common ancestor.

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8.11E: Fusobacteria

Fusobacterium are anaerobic, non-spore forming, gram-negative bacteria that are associated with periodontal disease and Lemierre's syndrome.

Learning Objectives

- Describe the role of Fusobacterium in Lemierre's syndrome

Key Points

- Fusobacterium flourish in anaerobic conditions.
- Fucosbacterium necrophorum are responsible for causing Lemierre's syndrome which is characterized by thrombophlebitis.
- Identification of Fusobacterium within the laboratory is difficult due to their asaccharolytic nature; however, advancements in molecular technology has resulted in identification of numerous species.

Key Terms

- **periodontal disease**: disease surrounding a tooth
- **asaccharolytic**: incapable of metabolizing carbohydrates
- **septicemia**: presence of pathogenic organisms in the bloodstream leading to sepsis

Fusobacteria are a genus of bacteria categorized as gram-negative with similarities to Bacteroides. Fusobacteria are rod-shaped bacilli capable of thriving in anaerobic conditions. However, in contrast to Bacteroides, Fusobacterium have a potent lipopolysaccharide that can function as an endotoxin. The Fusobacterium are associated with infection and disease including periodontal diseases, topical skin ulcers and Lemierres's syndrome. Fusobacterium are difficult to identify in the laboratory due to their asaccharolytic nature. However, the use of novel molecular biology techniques has allowed for the the identification of new species that are included in Fusobacterium. The diseases attributed to Fusobacterium infection involve symptoms that include tissue necrosis, septicemia, intra-amniotic infections and ulcers.

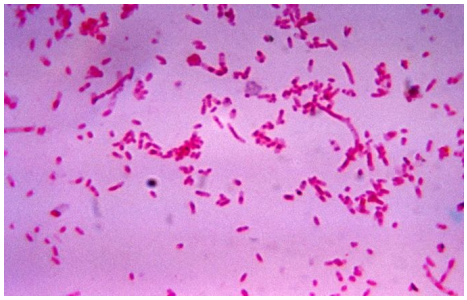

Figure: **Fusobacterium novum**: Image of a Fusobacterium cultured in a specific medium.

A specific disease caused by Fusobacteria includes Lemierres's syndrome. Lemierres's syndrome is also known as postanginal sepsis and is a form of thrombophlebitis. Thrombophlebitis is inflammation caused by a blood clot. In individuals infected with *Fusobacterium necrophorum* and additonal Fusobacterium as well, a sore develops in the throat due to infection by a bacterium of the Streptococcus genus. Once this sore develops into a peritonsillar abscess, the pocket is filled with pus and bacteria in close proximity to the tonsils. At this point, bacteria which are capable of thriving in anaerobic conditions, such as *Fusobacterium necrophorum* can flourish deep in the abscess. At this point, the bacteria are able to pass into the neighboring jugular vein and cause an infected clot to form. The bacteria are then able to circulate throughout the body via the bloodstream and pieces of the blood clot will dissociate from the original site and travel to the lungs. The pieces of the clot will settle in the lungs and block branches of the pulmonary artery, resulting in shortness of breath, chest pain and pneumonia. Fusobacteria are normal flora within the oropharyngeal and can clearly result in disease if conditions are optimal.

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8.11F: Spirochaetes

Spirochaetes are characterized by the presence of a double-membrane and long, spiral-shaped cells that are chemoheterotrophic.

Learning Objectives

- Outline the characteristics associated with spirochaetes and the associated diseases

Key Points

- Spirochaetes are chemoheterotrophic in nature and capable of thriving in anaerobic conditions.
- The spirochaetes are categorized by the presence of axial filaments which run lengthwise between the inner and outer membranes in periplasmic space.
- Spirochaetes are capable of causing diseases including leptospirosis, Lyme disease, relapsing fever and syphilis.

Key Terms

- **periplasmic**: surrounding the plasma of a bacterium

The spirochaetes belong to a phylum of distinctive double-membrane bacteria that are characterized by their long, spiral-shaped cells. The spirochaetes are chemoheterotrophic in nature, free-living and capable of thriving in anaerobic environments. They are often distinguished from other bacterial phyla by the location of their flagella. The flagella, in spirochaetes, runs lengthwise between the inner and outer membranes in the periplasmic space. Often referred to as axial filaments, there is a twisting motion that occurs which allows the spirochaete to move. During reproduction, the spirochaete is capable of undergoing asexual reproduction via binary fission. The binary fission allows for production of two separate spirochaetes.

The spirochaetes can be divided into three families which include: *Brachyspiraceae*, *Leptospiraceae*, and *Spirochaetaceae*. These families are all categorized under a single order, *Spirochaetales*. There are specific species of spirochaetes that are considered to be pathogenic. Some of the pathogenic species include:

- *Leptospira*, the cause of leptospirosis – leptospirosis is transmitted to humans from animals and a common form of transmission is by allowing contaminated water to come in contact with unhealed breaks in the skin, eyes and mucous membranes. The water becomes contaminated by coming into contact with the urine of an infected animal.
- *Borrelia burgdorferi*, *Borrelia garinii*, *Borrelia afzelii*, the cause of lyme-disease
- *Borrelia recurrentis*, the cause of relapsing fever
- *Treponema pallidum*, subspecies *pallidum*, the cause of syphilis
- *Treponema pallidum*, subspecies *pertenue*, the cause of yaws (tropical infection of the skin, bones and joints)
- *Brachyspira pilosicoli* and *Brachyspira aalborgi*, the cause of intestinal spirochetosis

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SECTION OVERVIEW

8.12: Thermophiles

Topic hierarchy

8.12A: Aquificales and Thermotogales

8.12B: Deinococcus and Thermus

8.12C: Chloroflexus and Relatives

8.12D: Nitrospirae and Deferribacter

8.12E: Aquifex, Thermocrinis, and Related Bacteria

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8.12A: Aquificales and Thermotogales

Along with Thermotogae, members of Aquificae are thermophilic eubacteria.

Learning Objectives

- Differentiate Aquificales from Thermotogae

Key Points

- The phylum Thermotogae is composed of gram-negative staining, anaerobic, mostly thermophilic, and hyperthermophilic bacteria.
- The Aquificae phylum is a diverse collection of bacteria that live in harsh environmental settings. They have been found in hot springs, sulfur pools, and thermal ocean vents.
- A 51 amino acid insertion has been identified in SecA preprotein translocase which is shared by various members of the phylum Aquificae as well as 2 Thermotoga species. The presence of the insertion in the Thermotoga species may be due to a horizontal gene transfer.
- However, a close relationship of the Aquificae to Thermotogae and the deep branching of Aquificae is not supported by phylogenetic studies based upon other gene/ protein sequences and also by conserved signature indels in several highly conserved universal proteins.

Key Terms

- **thermophile**: An organism — a type of extremophile — that thrives at relatively high temperatures, between 45 and 122 °C (113 and 252 °F). Many thermophiles are archaea. Thermophilic eubacteria are suggested to have been among the earliest bacteria.
- **hyperthermophile**: An organism that thrives in extremely hot environments— from 60 degrees C (140 degrees F) upwards. An optimal temperature for the existence of hyperthermophiles is above 80°C (176°F). Hyperthermophiles are a subset of extremophiles, micro-organisms within the domain Archaea, although some bacteria are able to tolerate temperatures of around 100°C (212°F), as well.

Along with Thermotogae, members of Aquificae are thermophilic eubacteria (thermophiles).

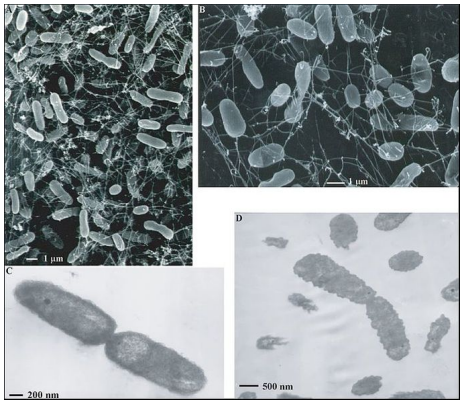

Figure: **Thermophile bacteria isolated from deep-sea vent fluids.**: This organism eats sulfur and hydrogen and fixes its own carbon from carbon dioxide. (A,B) scanning electron micrographs, and (C,D) transmission electron micrographs in thin sections.

Aquificales

The Aquificae phylum is a diverse collection of bacteria that live in harsh environmental settings. They have been found in hot springs, sulfur pools, and thermal ocean vents. Members of the genus Aquifex, for example, are productive in water between 85 to 95 °C. They are the dominant members of most terrestrial neutral to alkaline hot springs above 60 degrees Celsius. They are autotrophs, and are the primary carbon fixers in these environments. They are true bacteria (domain bacteria) as opposed to the other inhabitants of extreme environments, the Archaea.

Comparative genomic studies have identified six conserved signature indels (CSIs) that are specific for the species from the phylum Aquificae and provide potential molecular markers for this phylum. Additionally, a 51 amino acid insertion has been

identified in SecA preprotein translocase which is shared by various members of the phylum Aquificae as well as two Thermotoga species. The presence of the insertion in the Thermotoga species may be due to a horizontal gene transfer. In the 16S rRNA gene trees, the Aquificae species branch in the proximity of the phylum Thermotogae (another phylum comprising hyperthermophiles) close to the archaeal-bacterial branch point. However, a close relationship of the Aquificae to Thermotogae and the deep branching of Aquificae is not supported by phylogenetic studies based upon other gene/protein sequences and also by conserved signature indels in several highly conserved universal proteins.

Thermotogae

The phylum Thermotogae is composed of gram-negative staining, anaerobic, mostly thermophilic, and hyperthermophilic bacteria. The name of this phylum is derived from the existence of many of these organisms at high temperatures along with the characteristic sheath structure, or "toga," surrounding the cells of these species. Recently, some Thermotogae existing in mesophilic temperatures have also been identified. Although Thermotogae species exhibit Gram-negative staining, they are bounded by a single unit lipid membrane. Therefore, they are monoderm bacteria. Because of the ability of some Thermotogae species to thrive at high temperatures, they are considered attractive targets for use in industrial processes. The metabolic ability of Thermotogae to utilize different complex-carbohydrates for production of hydrogen gas led to these species being cited as a possible biotechnological source for production of energy alternative to fossil fuels.

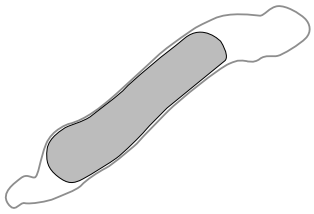

Figure: **Thermotoga sketch**: Outline of a Thermotoga maritima section showing the "toga. "

This phylum presently consists of a single class (Thermotogae), order (Thermotogales), and family (Thermotogaceae). It contains a total of nine genera (viz. Thermotoga, Petrotoga, Thermosipho, Fervidobacterium, Marinitoga, Kosmotoga, Geotoga, Thermopallium, and Thermococcoides), all of which are currently part of the family Thermotogaceae. In the 16S rRNA trees the Thermotogae have been observed to branch with the Aquificae in close proximity to the archaeal-bacterial branch point. The Thermotogae have also been scrutinized for their supposedly profuse lateral gene transfer (LGT) with Archaeal organisms. However, recent studies based on more robust methodologies suggest that incidence of LGT between Thermotogae and other groups including Archaea is not as high as suggested in earlier studies.

Until recently, no biochemical or molecular markers were known that could distinguish the species from the phylum Thermotogae from all other bacteria. However, a recent comparative genomic study has identified large numbers of conserved signature indels (CSIs) in important proteins that are specific for either all Thermotogae species or a number of its sub-groups. The newly discovered molecular markers provide novel means for identification and circumscription of species from the Thermotogae phylum in molecular terms and for future revisions to the taxonomy of this phylum.

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8.12B: Deinococcus and Thermus

Learning Objectives

- Compare Deinococcus and Thermus bacteria

DEINOCOCCUS

This is the one genus of three of the Deinococcales group from the Deinococcus-Thermus phylum, and is highly-resistant to environmental hazards. It has several species that are resistant to radiation (they have become famous for their ability to eat nuclear waste and other toxic materials), survive in the vacuum of space, and in extremes of heat and cold. There are 47 species of Deinococcus described according to NCBI on 25 August 2011.

These bacteria have thick cell walls that give them Gram-positive stains, but they include a second membrane and so are closer in structure to those of Gram-negative bacteria. Cavalier-Smith calls this clade *Hadobacteria* (from Hades, the Greek underworld).

They are also characterized by the presence of the carotenoid pigment Deinoxanthin that give them their pink color, and a high resistance to gamma and UV radiation. They are usually isolated according to these two criteria.

D. RADIODURANS

Deinococcus radiodurans is an extremophilic bacterium, one of the most radioresistant organisms known. It can survive cold, dehydration, vacuum, and acid, and is therefore known as a polyextremophile and has been listed as the world's toughest bacterium in *The Guinness Book of World Records*.

D. radiodurans is a rather large, spherical bacterium, with a diameter of 1.5 to 3.5 µm. Four cells normally stick together, forming a tetrad. The bacteria are easily cultured and do not appear to cause disease. Colonies are smooth, convex, and pink to red in color. D. radiodurans does not form endospores and is nonmotile. It is an obligate aerobic chemoorganoheterotroph, i.e., it uses oxygen to derive energy from organic compounds in its environment.

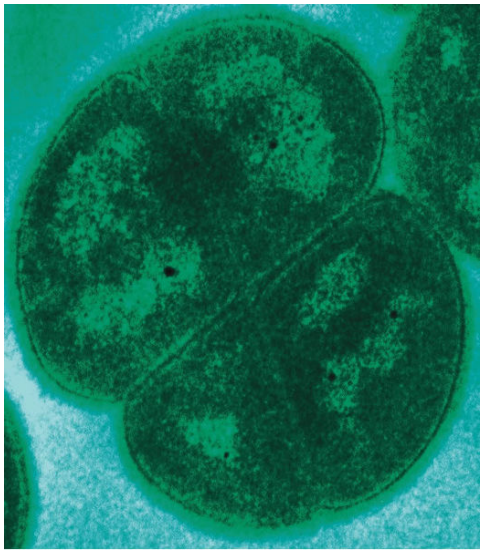

Figure: ***A tetrad of D. radiodurans****: Transmission electron micrograph (TEM) of D. radiodurans.*

It is often found in habitats rich in organic materials, such as soil, feces, meat, or sewage, but has also been isolated from dried foods, room dust, medical instruments and textiles. It is extremely resistant to ionizing radiation, ultraviolet light, desiccation, and oxidizing and electrophilic agents. Its genome consists of two circular chromosomes, one 2.65 million base pairs long and the other 412 thousand base pairs long, as well as a megaplasmid of 177 thousand base pairs and a plasmid of 46 thousand base pairs. It has about 3,195 genes. In its stationary phase, each bacterial cell contains four copies of this genome; when rapidly multiplying, this increases to eight to 10 copies.

D. radiodurans is capable of withstanding an acute dose of five thousand Gy (five hundred thousand rad) of ionizing radiation with almost no loss of viability, and an acute dose of 15 thousand Gy with 37% viability. A dose of five thousand Gy is estimated to

introduce several hundred double-strand breaks (DSBs) into the organism's DNA (~0.005 DSB/Gy/Mbp (haploid genome)). For comparison, a chest X-ray or Apollo mission involves about one mGy, five Gy can kill a human, two to eight hundred Gy will kill E. coli, and over four thousand Gy will kill the radiation-resistant tardigrade.

Several bacteria of comparable radioresistance are now known, including some species of the genus *Chroococcidiopsis* (phylum cyanobacteria) and some species of *Rubrobacter* (phylum actinobacteria); among the archaea, the species *Thermococcus gammatolerans* shows comparable radioresistance.

D. radiodurans also has a unique ability to repair damaged DNA. It isolates the damaged segments in a controlled area and repairs it. This bacteria can also repair many small fragments from an entire chromosome.

THERMUS

A genus of thermophilic bacteria that can tolerate high temperatures, it is one of several bacteria belonging to the Deinococcus-Thermus group and includes the following three species: *T. aquaticus*, *T. antranikianii*, and *T. igniterrae*. Thermus aquaticus is the source of the heat-resistant enzyme *Taq DNA polymerase*, one of the most important enzymes in molecular biology because of its use in the polymerase chain reaction (PCR) DNA-amplification technique.

It thrives at 70°C (160°F), but can survive at temperatures of 50°C to 80°C (120°F to 175°F). This bacterium is a chemotroph — it performs chemosynthesis to obtain food. However, since its range of temperature overlaps somewhat with that of the photosynthetic cyanobacteria that share its ideal environment, it is sometimes found living jointly with its neighbors, obtaining energy for growth from their photosynthesis.

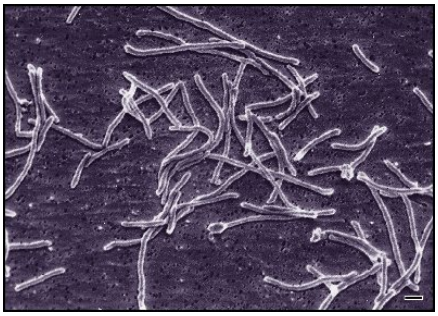

Figure: ***Thermus aquaticus****: Electron microscopy of thermus aquaticus.*

Key Points

- The Deinococcales include two families with three genera, *Deinococcus* and *Truepera*, the former with several species that are resistant to radiation; they are famous for their ability to eat nuclear waste and other toxic materials, survive in the vacuum of space and in extremes of heat and cold.
- The *Thermales* include several genera resistant to heat, including *Thermus*.
- These bacteria have thick cell walls that give them Gram-positive stains, but they include a second membrane and so are closer in structure to those of Gram-negative bacteria.

Key Terms

- **radioresistance**: Any form of resistance that an organism has to protect itself against the harmful effects of ionizing radiation
- **clade**: A group of animals or other organisms derived from a common ancestor species.
- **polyextremophile**: An organism which can tolerate two or more extreme environmental factors.

The *Deinococcus-Thermus* are a small group of bacteria composed of cocci that are highly-resistant to environmental hazards. There are two main groups: the Deinococcales include two families, with three genera, Deinococcus and Truepera.

The *Thermales* include several genera resistant to heat (Marinithermus, Meiothermus, Oceanithermus, Thermus, Vulcanithermus).

Though these two groups evolved from a common ancestor, the two mechanisms of resistance appear to be largely independent.

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8.12C: Chloroflexus and Relatives

Learning Objectives

- Show the unique features of chloroflexus

As a genus, Chloroflexus spp. are Gram-negative filamentous anoxygenic phototrophic (FAP) organisms that utilize type II photosynthetic reaction centers containing bacteriochlorophyll a similar to the purple bacteria, and light-harvesting chlorosomes containing bacteriochlorophyll c similar to green sulfur bacteria of the Chlorobi. As the name implies, these anoxygenic phototrophs do not produce oxygen as a byproduct of photosynthesis, in contrast to oxygenic phototrophs such as cyanobacteria, algae, and higher plants. While oxygenic phototrophs use water as an electron donor for phototrophy, Chloroflexus uses reduced sulfur compounds such as hydrogen sulfide, thiosulfate, or elemental sulfur. This belies their antiquated name green non-sulfur bacteria. However, Chloroflexus spp. can also utilize hydrogen (H2) as a source of electrons.

Chloroflexus aurantiacus is thought to grow photoheterotrophically in nature, but it has the capability of fixing inorganic carbon through photoautotrophic growth. Instead of using the Calvin-Benson-Bassham Cycle typical of plants, Chloroflexus aurantiacus has been demonstrated to use a novel autotrophic pathway known as the 3-Hydroxypropionate pathway.The complete electron transport chain for Chloroflexus spp. is not yet known. Particularly, *Chloroflexus aurantiacus* has not been demonstrated to have a cytochrome bc1 complex. It may use different proteins to reduce cytochrome c.

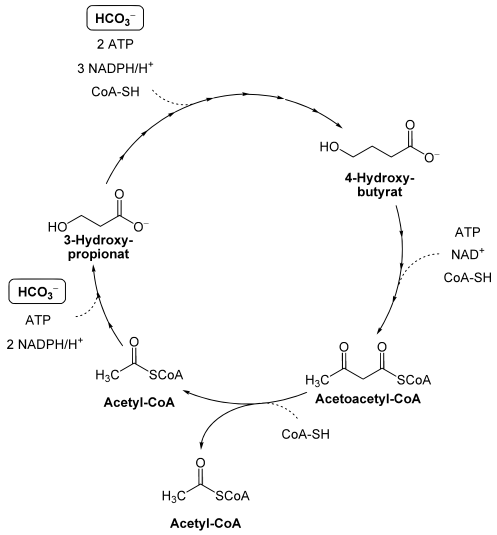

Figure: ***3-Hydroxypropionate Pathway**: A schematic representation of the 3-Hydroxypropionate CO2 assimilatory pathway observed in Chloroflexus bacteria.*

Chloroflexus aurantiacus is a photosynthetic bacterium isolated from hot springs, belonging to the green non-sulfur bacteria. This organism is thermophilic and can grow at temperatures from 35 °C to 70 °C. Chloroflexus aurantiacus can survive in the dark if oxygen is available. When grown in the dark, Chloroflexus aurantiacus has a dark orange color. When grown in sunlight it is dark green. The individual bacteria tend to form filamentous colonies enclosed in sheaths, which are known as trichomes. One of the main reasons for interest in Chloroflexus aurantiacus is in the study of the evolution of photosynthesis.

How did photosynthesis arise in bacteria? The answer to this question is complicated by the fact that there are several types of light-harvesting energy capture systems. Chloroflexus aurantiacus has been of interest in the search for origins of the so-called type II photosynthetic reaction center. One idea is that bacteria with respiratory electron transport evolved photosynthesis by coupling a light-harvesting energy capture system to the pre-existing respiratory electron transport chain. Therefore, rare organisms like Chloroflexus aurantiacus that can survive using either respiration or photosynthesis are of interest in on-going attempts to trace the evolution of photosynthesis.

The Chloroflexi or Chlorobacteria are a phylum of bacteria containing isolates with a diversity of phenotypes including members that are aerobic thermophiles, which use oxygen and grow well in high temperatures, anoxygenic phototrophs, which use light for photosynthesis, and anaerobic halorespirers, which use halogenated organics (such as the toxic chlorinated ethenes and polychlorinated biphenyls) as energy sources. Whereas most bacteria, in terms of diversity, are diderms and stain Gram negative

with the exception of the Firmicutes (low CG Gram positives), Actinobacteria (high CG gram positives), and the Deinococcus-Thermus group (Gram positive, but diderms with thick peptidoglycan), the members of the phylum Chloroflexi are monoderms and stain mostly Gram negative.

In 1987, Carl Woese, regarded as the forerunner of the molecular phylogeny revolution, divided Eubacteria into 11 divisions based on 16S ribosomal RNA (SSU) sequences and grouped the genera Chloroflexus, Herpetosiphon, and Thermomicrobium into the "Green non-sulfur bacteria and relatives," which was temporarily renamed as "Chloroflexi" in Volume One of Bergey's Manual of Systematic Bacteriology.

Recent phylogenetic analysis of the Chloroflexi has found very weak support for the grouping together of the different classes currently part of the phylum. The six classes that make up the phylum did not consistently form a well-supported monophyletic clade in phylogenetic trees based on concatenated sequences for large datasets of proteins. No conserved signature indels were identified that were uniquely shared by the entire phylum. However, the classes "Chloroflexi" and Thermomicrobia were found to group together consistently by both phylogenetic means and the identification of shared conserved signature indels in the 50S ribosomal protein L19 and the enzyme UDP-glucose 4-epimerase. It has been suggested that the phylum Chloroflexi "sensu stricto" should comprise only the classes Chloroflexi and Thermomicrobia, and the other four classes ("Dehalococcoidetes," Anaerolineae, Caldilineae, and Ktedonobacteria) may represent one or more independent phyla branching in the neighborhood of the Chloroflexi.

Key Points

- These anoxygenic phototrophs do not produce oxygen as a byproduct of photosynthesis, in contrast to oxygenic phototrophs like cyanobacteria. While oxygenic phototrophs use water as an electron donor for phototrophy, Chloroflexus uses reduced sulfur compounds such as thiosulfate or elemental sulfur.
- The complete electron transport chain for Chloroflexus spp. is not yet known. Particularly, Chloroflexus aurantiacus has not been demonstrated to have a cytochrome bc1 complex, and may use different proteins to reduce cytochrome c.
- The Chloroflexi are a phylum of bacteria containing isolates with a diversity of phenotypes including aerobic thermophiles, which use oxygen and grow well in high temperatures, anoxygenic phototrophs, which use light for photosynthesis, and anaerobic halorespirers, which uses halogenated organics.
- Recent phylogenetic analysis of the Chloroflexi has found very weak support for the grouping together of the different classes currently part of the phylum.

Key Terms

- **trichome**: Certain (usually filamentous) algae have the terminal cell produced into an elongate "hair-like" structure called a trichome. The same term is applied to such structures in some cyanobacteria.

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8.12D: Nitrospirae and Deferribacter

Learning Objectives

- Describe nitrospirae

Nitrospirae is a phylum of bacteria containing only one class: *Nitrospira*, which itself contains one order: *Nitrospirales*, and one family: *Nitrospiraceae*. However, it includes multiple genera, the largest of which is *Nitrospira*. The first member of this phylum, *Nitrospira marina*, was discovered in 1986 by Watson et al., isolated from the Gulf of Maine. The second member of this phylum, *Thermodesulfovibrio yellowstonii*, was discovered in 1994. The third, *Nitrospira moscoviensis*, was discovered in 1995 from a corroded iron pipe in a Moscow heating system. It is a Gram-negative nitrite-oxidizing organism with a helical to vibroid morphology 0.9-2.2 x 0.2-0.4 micrometers in size.

Some nitrospirae species perform important functions in the Nitrogen Cycle. The Nitrogen Cycle describes the changes in nitrogenous compounds in the environment. Because many of them are toxic, it is important to know something about this cycle. Luckily, these compounds are converted to less and less toxic forms through this Nitrogen Cycle.

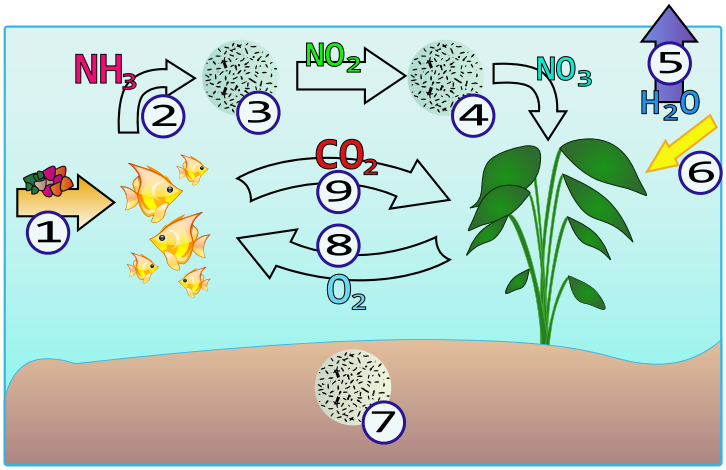

Figure: ***Nitrogen cycle in aquarium****: Legend: (1) Addition of food and nutrients, (2) Production of urea and ammonia by fish, (3) Ammonia is converted to nitrites by beneficial nitrosomonas bacteria, (4) Nitrites are converted to nitrates by beneficial nitrospira bacteria. Less toxic nitrates are removed by plants and periodic water changes. (5) Evaporation. (6) Light. (7) Soil. (8) O2 produced by plants. (9) CO2 produced by fish.*

To simplify, if you start with your organisms, they release a compound, ammonia, as a waste product or a product of decomposition. Ammonia is both quite toxic and dangerous. By a process known as *nitrification*, bacteria convert these waste products to less toxic forms. These bacteria live in aerobic conditions and benefit from the presence of oxygen. First the ammonia is converted to nitrites by Nitrosomonas; this compound is still toxic. Next, nitrites are converted to nitrates by Nitrobacter or Nitrospira. Nitrates are much less toxic compared to ammonia and nitrite. In an environment with a healthy colony of these nitrifying bacteria, ammonia and nitrites levels will reach zero.

Deferribacter is a genus in the phylum *Deferribacteres* (Bacteria).The genus contains 4 species:

- *D. abyssi*
- *D. autotrophicus*
- *D. desulfuricans*
- *D. thermophilus*

Key Points

- Nitrospirae is a phylum of bacteria. It contains only one class, (Nitrospira), which itself contains one order (Nitrospirales), and one family (Nitrospiraceae). It includes multiple genera, such as Nitrospira, the largest. The first member of this phylum, Nitrospira marina, was discovered in 1985.
- Nitrospira is a genus of bacteria in the phylum Nitrospirae. The second member of this genus was discovered in 1995 from a corroded iron pipe in a Moscow heating system.
- In the nitrogen cycle, nitrites are converted to nitrates by Nitrobacter or Nitrospira.

- Deferribacter is a genus in the phylum Deferribacteres (Bacteria).The genus contains 4 species.

Key Terms

- **nitrogen cycle**: The natural circulation of nitrogen, in which atmospheric nitrogen is converted to nitrogen oxides by lightning and deposited in the soil by rain where it is assimilated by plants and either eaten by animals (and returned as feces) or decomposed back to elemental nitrogen by bacteria.

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8.12E: Aquifex, Thermocrinis, and Related Bacteria

Learning Objectives

- Outline the similarities of Aquifex, Thermocrinis and related bacteria

The *Aquificae* phylum is a diverse collection of bacteria that live in harsh environmental settings. They have been found in hot springs, sulfur pools, and thermal ocean vents.Members of the genus *Aquifex*, for example, are productive in water between 85 to 95 °C. They are the dominant members of most terrestrial neutral-to-alkaline hot springs above 60 °C. They are autotrophs, and the primary carbon fixers in these environments. They are true bacteria (domain bacteria).

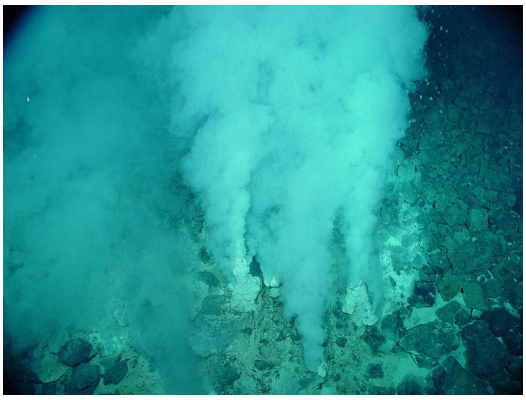

Figure: ***Aquificae habitat****: White flocculent mats in and around the extremely gassy, high-temperature (>100°C, 212°F) white smokers at Champagne Vent.*

Comparative genomic studies have identified six conserved signature indels (CSIs) that are specific for the species from the phylum Aquificae and provide potential molecular markers for it. Along with *Thermotogae*, members of Aquificae are thermophilic eubacteria.

A 51 amino acid insertion has been identified in SecA preprotein translocase which is shared by various members of the phylum Aquificae as well as two Thermotogae species. The presence of the insertion in the Thermotogae species may be due to a horizontal gene transfer. In the 16S rRNA gene trees, the Aquificae species branch in the proximity of the phylum Thermotogae (another phylum comprising hyperthermophilic organisms) close to the archaeal-bacterial branch point. However, a close relationship of the Aquificae to Thermotogae, and the deep branching of Aquificae, is not supported by phylogenetic studies based upon other gene/protein sequences and also by conserved signature indels in several highly-conserved universal proteins. The Aquificaceae family in the phylum Aquificae contains contains five genera, including *Aquifex* and *Thermocrinis*.

Aquifex is a genus of bacteria, one of the few in the phylum Aquificae. The two species generally classified in Aquifex are *A. pyrophilus* and *A. aeolicus*. Both are highly thermophilic, growing best in water temperature of 85 °C to 95 °C. Both known species are rod-shaped bacteria with a length of two to six µm and a diameter of around 0.5 µm. They are non-sporeforming, Gram-negative autotrophs. Aquifex means “water-maker” in Latin, and refers to the fact that its method of respiration creates water. They tend to form cell aggregates composed of up to one hundred individual cells. A. pyrophilus can even grow anaerobically by reducing nitrogen instead of oxygen. Like other thermophilic bacteria, Aquifex has important uses in industrial processes.

The genome of *A. aeolicus* has been successfully mapped. This was made easier by the fact that the length of the genome is only about a third of that for E. coli. Comparison of the A. aeolicus genome to other organisms showed that around 16% of its genes originated from the Archaea domain. Members of this genus are thought to be some of the earliest members of the eubacteria domain. *A. aeolicus* was discovered north of Sicily, while *A. pyrophilus* was first found just north of Iceland. A. aeolicus is also known as one of the few bacterial species capable of doing gene silencing.

Key Points

- Along with *Thermotogae*, members of *Aquificae* are thermophilic eubacteria. The *Aquificaceae* family in the phylum *Aquificae* contains five genera, including *Aquifex* and *Thermocrinis*.
- *Aquifex* is a genus of bacteria, one of the few in the phylum *Aquificae*. The two species generally classified in Aquifex are *A. pyrophilus* and *A. aeolicus.* Both are highly thermophilic, growing best in water temperature of 85 °C to 95 °C.

- The genome of *A. aeolicus* has been successfully mapped. Comparison of its genome to other organisms showed that around 16% of its genes originated from the *Archaea* domain. Members of this genus are thought to be some of the earliest members of the eubacteria domain.

Key Terms

- **indel**: Either an insertion or deletion mutation in the genetic code.
- **gene silencing**: Any technique or mechanism in which the expression of a gene is prevented.

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SECTION OVERVIEW

8.13: Archaeal Diversity

Topic hierarchy

8.13A: Energy Conservation and Autotrophy in Archaea

8.13B: Archaeal Gene Regulation

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8.13A: Energy Conservation and Autotrophy in Archaea

Archaea can use a number of different mechanisms to get nutrients and energy.

Learning Objectives

- Discuss archaea energy sources

Key Points

- Lithotrophic archaea use non- organic sources to live.
- Phototrophic archaea use light in a non-photosynthetic fashion to drive ion pumps needed to survive.
- Archaeal energy sources are extremely diverse, including light, metallic ions, and even acidic (pH)-dependent sources.

Key Terms

- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.
- **calvin cycle**: A series of biochemical reactions that take place in the stroma of chloroplasts in photosynthetic organisms.

Archaea exhibit a variety of chemical reactions in their metabolism and use many sources of energy. These reactions are classified into nutritional groups, depending on energy and carbon sources. Some archaea, called lithotrophs, obtain energy from inorganic compounds such as sulfur or ammonia. Other examples include nitrifiers, methanogens, and anaerobic methane oxidizers. In these reactions one compound passes electrons to another in a redox reaction, releasing energy to fuel the cell's activities. One compound acts as an electron donor and one as an electron acceptor. The energy released generates adenosine triphosphate (ATP) through chemiosmosis in the same basic process that happens in the mitochondrion of eukaryotic cells.



Figure: **Archaea in an Extreme Environment**: Archaea can live in extreme environments and live off autotrophic sources. Here archaea were found living under highly acidic conditions, in the runoff from an iron mine.

Many basic metabolic pathways are shared between all forms of life. For example, archaea use a modified form of glycolysis (the Entner–Doudoroff pathway) and either a complete or partial citric acid cycle. These similarities to other organisms probably reflect both early origins in the history of life and their high level of efficiency.

Some Euryarchaeota are methanogens living in anaerobic environments such as swamps. This form of metabolism evolved early, and it is possible that the first free-living organism was a methanogen. A common reaction in methanogens involves the use of carbon dioxide as an electron acceptor to oxidize hydrogen. Methanogenesis uses a range of coenzymes that are unique to these archaea, such as coenzyme M and methanofuran. Other organic compounds such as alcohols, acetic acid, or formic acid are used as alternative electron acceptors by methanogens. These reactions are common in gut-dwelling archaea. Acetotrophic archaea also break down acetic acid into methane and carbon dioxide directly. These acetotrophs are archaea in the order Methanosarcinales, and are a major part of the communities of microorganisms that produce biogas.

Other archaea, called autotrophs, use CO_2 in the atmosphere as a source of carbon, in a process called carbon fixation. This process involves either a highly modified form of the Calvin cycle or a recently discovered metabolic pathway called the 3-hydroxypropionate/4-hydroxybutyrate cycle. In addition, the Crenarchaeota use the reverse Krebs cycle while the Euryarchaeota use the reductive acetyl-CoA pathway. Carbon–fixation is powered by inorganic energy sources.

Phototrophic archaea use sunlight as a source of energy; however, oxygen–generating photosynthesis does not occur in any archaea. Instead, in archaea such as the Halobacteria, light-activated ion pumps generate ion gradients by pumping ions out of the cell across the plasma membrane. The energy stored in these electrochemical gradients is then converted into ATP by ATP synthase. This process is a form of photophosphorylation. The ability of these light-driven pumps to move ions across membranes depends on light-driven changes in the structure of a retinol cofactor buried in the center of the protein.

Besides these, archaeal energy sources are extremely diverse, and range from the oxidation of ammonia by the Nitrosopumilales to the oxidation of hydrogen sulfide or elemental sulfur by species of Sulfolobus, using either oxygen or metal ions as electron acceptors.

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8.13B: Archaeal Gene Regulation

Archaea are very different genetically from bacteria and eukaryotes.

Learning Objectives

- Describe the unique features of archaea

Key Points

- Like bacteria and eukaryotes, archaea can be infected by viruses.
- Many unique proteins are encoded by archaea, many of these proteins have unknown functions.
- Introns are more rare than eukaryotic species, and additionally unlike eukaryotes the introns usually do not reside in protein coding genes but rather rRNA and tRNA.

Key Terms

- **intron**: A portion of a split gene that is included in pre-RNA transcripts but is removed during RNA processing and rapidly degraded.
- **ribosome**: Small organelles found in all cells; involved in the production of proteins by translating messenger RNA.
- **polymerase**: Any of various enzymes that catalyze the formation of polymers of DNA or RNA using an existing strand of DNA or RNA as a template.

Archaea usually have a single circular chromosome, the size of which may be as great as 5,751,492 base pairs in Methanosarcina acetivorans, the largest known archaean genome. One-tenth of this size is the tiny 490,885 base-pair genome of Nanoarchaeum equitans, the smallest archaean genome known. It is estimated to contain only 537 protein-encoding genes. Smaller independent pieces of DNA, called plasmids, are also found in archaea. Plasmids may be transferred between cells by physical contact, in a process that may be similar to bacterial conjugation.

Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes, including bottles, hooked rods, or teardrops. These viruses have been studied in most detail in thermophilics, particularly the orders Sulfolobales and Thermoproteales. Two groups of single-stranded DNA viruses that infect archaea have been recently isolated. One group is exemplified by the Halorubrum pleomorphic virus 1 (“Pleolipoviridae”) infecting halophilic archaea and the other one by the Aeropyrum coil-shaped virus (“Spiraviridae”) infecting a hyperthermophilic (optimal growth at 90-95°C) host. Notably, the latter virus has the largest currently reported ssDNA genome. Defenses against these viruses may involve RNA interference from repetitive DNA sequences that are related to the genes of the viruses.

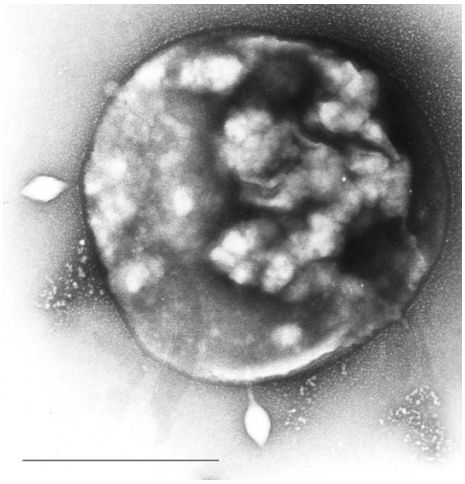

Figure: **Archaeal viral infection**: Cell of Sulfolobus infected by virus STSV1 observed under microscopy. Two spindle-shaped viruses were being released from the host cell. The strain of Sulfolobus and STSV1 (Sulfolobus tengchongensis Spindle-shaped Virus 1) were isolated by Xiaoyu Xiang and his colleagues in an acidic hot spring in Yunnan Province, China. At present, STSV1 is the largest archaeal virus to have been isolated and studied. Its genome sequence has been sequenced.

Archaea are genetically distinct from bacteria and eukaryotes, with up to 15% of the proteins encoded by any one archaeal genome being unique to the domain, although most of these unique genes have no known function. Of the remainder of the unique proteins

that have an identified function, most belong to the Euryarchaea and are involved in methanogenesis. The proteins that archaea, bacteria, and eukaryotes share form a common core of cell function, relating mostly to transcription, translation, and nucleotide metabolism. Other characteristic archaean features are the organization of genes of related function—such as enzymes that catalyze steps in the same metabolic pathway into novel operons, and large differences in tRNA genes and their aminoacyl tRNA synthetases.

Transcription and translation in archaea resemble these processes in eukaryotes more than in bacteria, with the archaean RNA polymerase and ribosomes being very close to their equivalents in eukaryotes. Although archaea only have one type of RNA polymerase, its structure and function in transcription seems to be close to that of the eukaryotic RNA polymerase II, with similar protein assemblies (the general transcription factors) directing the binding of the RNA polymerase to a gene's promoter. However, other archaean transcription factors are closer to those found in bacteria. Post-transcriptional modification is simpler than in eukaryotes, since most archaean genes lack introns, although there are many introns in their transfer RNA and ribosomal RNA genes, and introns may occur in a few protein-encoding genes.

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SECTION OVERVIEW

8.14: Crenarchaeota

The Crenarchaeota are archaea that have been classified as a phylum of the Archaea domain.

Topic hierarchy

8.14A: Habitats and Energy Metabolism of Crenarchaeota

8.14B: Hyperthermophiles from Terrestrial Volcanic Habitats

8.14C: Hyperthermophiles from Submarine Volcanic Habitats

8.14D: Nonthermophilic Crenarchaeota

8.14E: Psychrophilic Crenarchaeota

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8.14A: Habitats and Energy Metabolism of Crenarchaeota

Crenarchaeota exist in a wide range of habitats and exhibit a great variety of chemical reactions in their metabolism.

Learning Objectives

- Outline the various types of energy metabolism used by Crenarchaeota

Key Points

- The first-discovered archaeans were extremophiles.
- Extremophile archaea are members of four main physiological groups: halophiles, thermophiles, alkaliphiles, and acidophiles.
- Some archaea obtain energy from inorganic compounds such as sulfur or ammonia (they are lithotrophs).
- Other groups of archaea use sunlight as a source of energy (phototrophs) or CO2 in the atmosphere as a source of carbon (autotrophs).

Key Terms

- **extremophile**: An organism that lives under extreme conditions of temperature, salinity, and so on. They are commercially important as a source of enzymes that operate under similar conditions.
- **phototroph**: An organism that carries out photon capture to acquire energy. They use the energy from light to carry out various cellular metabolic processes.
- **autotroph**: Any organism that can synthesize its food from inorganic substances, using heat or light as a source of energy.

The Crenarchaeota are Archaea that have been classified as either a phylum of the Archaea kingdom, or in a kingdom of its own. Archaea exist in a broad range of habitats, and as a major part of global ecosystems, they may contribute up to 20% of earth's biomass.

The first-discovered archaeans were extremophiles. Indeed, some archaea survive high temperatures, often above 100 °C (212 °F), as found in geysers, black smokers, and oil wells. Other common habitats include very cold habitats and highly saline, acidic, or alkaline water. However, archaea also include mesophiles that grow in mild conditions, in marshland, sewage, the oceans, and soils.

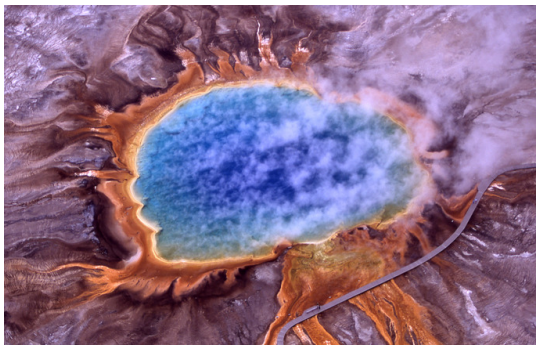

Figure: **Microbial Mats Around the Grand Prismatic Spring**: Thermophiles produce some of the bright colors of Grand Prismatic Spring, Yellowstone National Park

Extremophile archaea are members of four main physiological groups. These are the:

- halophiles
- thermophiles
- alkaliphiles
- acidophiles

These groups are not comprehensive or phylum-specific, nor are they mutually exclusive, since some archaea belong to several groups. Nonetheless, they are a useful starting point for classification Halophiles live in extremely saline environments such as salt lakes. Thermophiles grow best at temperatures above 45 °C (113 °F), in places such as hot springs; hyperthermophilic archaea grow optimally at temperatures greater than 80 °C (176 °F). Other archaea exist in very acidic or alkaline conditions.

Recently, several studies have shown that archae exist not only in mesophilic and thermophilic environments but are also present, sometimes in high numbers, at low temperatures as well, as found in cold oceanic environments.

Chemical reactions and energy sources

Archaea exhibit a great variety of chemical reactions in their metabolism and use many sources of energy. These reactions are classified into nutritional groups, depending on energy and carbon sources.

Some archaea obtain *energy from inorganic compounds* such as sulfur or ammonia (they are lithotrophs). These include nitrifiers, methanogens and anaerobic methane oxidisers. In these reactions one compound passes electrons to another (in a redox reaction), releasing energy to fuel the cell's activities. One compound acts as an electron donor and one as an electron acceptor. The energy released generates adenosine triphosphate (ATP) through chemiosmosis, in the same basic process that happens in the mitochondrion of eukaryotic cells.

Other groups of archaea use *sunlight as a source of energy* (phototrophs). However, oxygen–generating photosynthesis does not occur in any of these organisms. Many basic metabolic pathways are shared between all forms of life; for example, archaea use a modified form of glycolysis (the Entner–Doudoroff pathway) and either a complete or partial citric acid cycle. These similarities to other organisms probably reflect both early origins in the history of life and their high level of efficiency.

Some Euryarchaeota are *methanogens* living in anaerobic environments such as swamps. This form of metabolism evolved early, and it is even possible that the first free-living organism was a methanogen. A common reaction involves the use of carbon dioxide as an electron acceptor to oxidize hydrogen. Methanogenesis involves a range of coenzymes that are unique to these archaea, such as coenzyme M and methanofuran. These reactions are common in gut-dwelling archaea. Acetic acid is also broken down into methane and carbon dioxide directly, by acetotrophic archaea. These acetotrophs are archaea in the order Methanosarcinales, and are a major part of the communities of microorganisms that produce biogas.

Other archaea use *CO2* in the atmosphere as a source of carbon, in a process called carbon fixation (they are autotrophs). This process involves either a highly modified form of the Calvin cycle or a recently discovered metabolic pathway called the 3-hydroxypropionate/4-hydroxybutyrate cycle. The Crenarchaeota also use the reverse Krebs cycle while the Euryarchaeota also use the reductive acetyl-CoA pathway. Carbon–fixation is powered by inorganic energy sources. No known archaea carry out photosynthesis.

Archaeal energy sources are extremely diverse, and range from the oxidation of ammonia by the Nitrosopumilales to the oxidation of hydrogen sulfide or elemental sulfur by species of Sulfolobus, using either oxygen or metal ions as electron acceptors.

Phototrophic archaea use *light to produce chemical energy* in the form of ATP. In the Halobacteria, light-activated ion pumps like bacteriorhodopsin and halorhodopsin generate ion gradients by pumping ions out of the cell across the plasma membrane. The energy stored in these electrochemical gradients is then converted into ATP by ATP synthase (photophosphorylation).

Some marine Crenarchaeota are capable of *nitrification*, suggesting these organisms may affect the oceanic nitrogen cycle, although these oceanic Crenarchaeota may also use other sources of energy. Vast numbers of archaea are also found in the sediments that cover the sea floor, with these organisms making up the majority of living cells at depths over 1 meter below the ocean bottom.

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8.14B: Hyperthermophiles from Terrestrial Volcanic Habitats

A hyperthermophile thrives at relatively high temperatures and can be found in geothermally heated regions of the Earth.

Learning Objectives

- Summarize the traits that define Hyperthermophiles

Key Points

- Unlike other types of bacteria, thermophiles can survive at much hotter temperatures, whereas other bacteria would be damaged or killed if exposed to the same temperatures.
- Thermophiles contain enzymes that can function at high temperatures.
- Hyperthermophiles are particularly extreme thermophiles for which the optimal temperatures are above 80°C, and their membranes and proteins are unusually stable at these extremely high temperatures.

Key Terms

- **lithotroph**: An organism that obtains its energy from inorganic compounds (such as ammonia) via electron transfer.
- **thermophile**: An organism that lives and thrives at relatively high temperatures; a form of extremophile; many are members of the Archaea.

A thermophile is an organism —a type of extremophile—that thrives at relatively high temperatures, between 45 and 122 °C (113 and 252 °F). Many thermophiles are archaea. Thermophilic eubacteria are suggested to have been among the earliest bacteria. Thermophiles are found in various geothermally heated regions of the Earth, such as the hot springs found in Yellowstone National Park.

Unlike other types of bacteria, thermophiles can survive at much hotter temperatures, whereas other bacteria would be damaged or killed if exposed to the same temperatures. As a prerequisite for their survival, thermophiles contain enzymes that can function at high temperatures. Some of these enzymes are used in molecular biology (for example, heat-stable DNA polymerases for PCR), and in washing agents. Thermophiles are classified into obligate and facultative thermophiles; obligate thermophiles (also called extreme thermophiles) require such high temperatures for growth, whereas facultative thermophiles (also called moderate thermophiles) can thrive at high temperatures, but also at lower temperatures (below 50°C).

Hyperthermophiles are particularly extreme thermophiles for which the optimal temperatures are above 80°C. Thermophiles, meaning “heat-loving,” are organisms with an optimum growth temperature of 50°C or more, a maximum of up to 70°C or more, and a minimum of about 40°C, but these are only approximate. Some extreme thermophiles (hyperthermophiles) require a very high temperature (80°C to 105°C) for growth. Their membranes and proteins are unusually stable at these extremely high temperatures. Thus, many important biotechnological processes use thermophilic enzymes because of their ability to withstand intense heat.

Many of the hyperthermophiles Archea require elemental sulfur for growth. Some are anaerobes that use the sulfur instead of oxygen as an electron acceptor during cellular respiration. Some are lithotrophs that oxidize sulfur to sulfuric acid as an energy source, thus requiring the microorganism to be adapted to very low pH (i.e., it is an acidophile as well as thermophile). These organisms are inhabitants of hot, sulfur-rich environments usually associated with volcanism, such as hot springs, geysers, and fumaroles. In these places, especially in Yellowstone National Park, zonation of microorganisms according to their temperature optima occurs. Often, these organisms are colored due to the presence of photosynthetic pigments.

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8.14C: Hyperthermophiles from Submarine Volcanic Habitats

Hyperthermophiles live in dark regions of the oceans and use chemosynthesis to produce biomass from single carbon molecules.

Learning Objectives

- Describe the metabolic processes used by hyperthermophiles found in submarine volcanic habitats

Key Points

- Chemosynthesis is the biological conversion of one or more carbon molecules and nutrients into organic matter using the oxidation of inorganic molecules (e.g. hydrogen gas, hydrogen sulfide) or methane as a source of energy.
- The energy for chemosynthesis can be derived from hydrogen, hydrogen sulfide or ammonia.
- Many chemosynthetic microorganisms are consumed by other organisms in the ocean, and symbiotic associations between chemosynthesizers and respiring heterotrophs are quite common.

Key Terms

- **hydrothermal vent**: a hot spring, on the floor of the ocean, mostly along the central axes of the mid-ocean ridges, where heated fluids emerge from fissures in the Earth's crust
- **symbiotic**: Of a relationship with mutual benefit between two individuals or organisms.
- **chemosynthesis**: The production of carbohydrates and other compounds from simple compounds such as carbon dioxide, using the oxidation of chemical nutrients as a source of energy rather than sunlight; it is limited to certain bacteria and fungi.

In biochemistry, chemosynthesis is the biological conversion of one or more carbon molecules (usually carbon dioxide or methane) and nutrients into organic matter using the oxidation of inorganic molecules (e.g. hydrogen gas, hydrogen sulfide) or methane as a source of energy. Chemoautotrophs, organisms that obtain carbon through chemosynthesis, are phylogenetically diverse. Groups that include conspicuous or biogeochemically-important taxa include the sulfur-oxidizing gamma and epsilon proteobacteria, the Aquificaeles, the methanogenic archaea and the neutrophilic iron-oxidizing bacteria.

A thermophile is an organism that thrives at relatively high temperatures, between 45 and 122 °C (113 and 252 °F). Thermophiles are found in various geothermally heated regions of the Earth, such as deep sea hydrothermal vents. As a prerequisite for their survival, thermophiles contain enzymes that can function at high temperatures. Some of these enzymes are used in molecular biology (for example, heat-stable DNA polymerases for PCR), and in washing agents.

Thermophiles are classified into obligate and facultative thermophiles: Obligate thermophiles (also called extreme thermophiles) require such high temperatures for growth, whereas facultative thermophiles (also called moderate thermophiles) can thrive at high temperatures, but also at lower temperatures (below 50°C). For example, Venenivibrio stagnispumantis gains energy by oxidizing hydrogen gas.

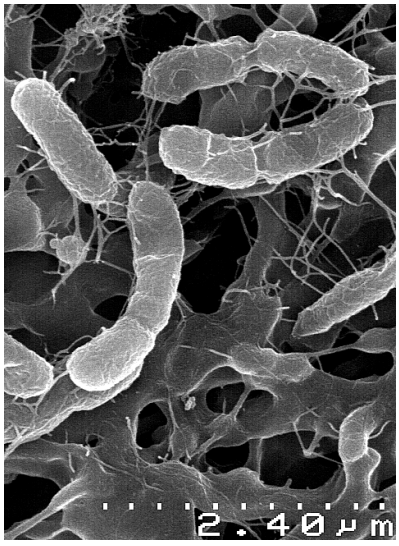

Figure: **Venenivibrio**: Scanning Electron Microscopy image of Venenivibrio stagnispumantis, a species which gains energy by oxidizing hydrogen gas.

Many microorganisms in dark regions of the oceans also use chemosynthesis to produce biomass from single carbon molecules. Two categories can be distinguished. In the rare sites at which hydrogen molecules (H2) are available, the energy available from the reaction between CO2 and H2 (leading to production of methane, CH4) can be large enough to drive the production of biomass. Alternatively, in most oceanic environments, energy for chemosynthesis derives from reactions in which substances such as hydrogen sulfide or ammonia are oxidized to produce formaldehyde (which will be used to make carbohydrates) and solid globules of sulfur. This may occur with or without the presence of oxygen. In bacteria that can do this, such as purple sulfur bacteria, yellow globules of sulfur are present and visible in the cytoplasm.

Many chemosynthetic microorganisms are consumed by other organisms in the ocean, and symbiotic associations between chemosynthesizers and respiring heterotrophs are quite common. Large populations of animals can be supported by chemosynthetic secondary production at hydrothermal vents, methane clathrates, cold seeps, whale falls, and isolated cave water. Indeed, it has been hypothesized that chemosynthesis may support life below the surface of Mars, Jupiter's moon Europa, and other planets. Giant tube worms use bacteria in their trophosome to react hydrogen sulfide with oxygen as a source of energy.

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8.14D: Nonthermophilic Crenarchaeota

Nonthermophilic Crenarchaeota can be extreme halophiles living in highly salty environments.

Learning Objectives

- Discuss the characteristics of nonthermophilic crenarchaeota, specifically Halococcus, that allow it to survive in extreme environments

Key Points

- Halococcus is a genus of extreme halophilic archaea.
- Halophiles are found mainly in inland bodies of water with high salinity, where their pigments (from a protein called rhodopsinprotein) tint the sediment bright colors.
- Halococcus and similar halophilic organisms have been utilized economically in the food industry and even in skin-care production.
- Halococcus is able to survive in its high-saline habitat by preventing the dehydration of its cytoplasm using a solute which is either found in their cell structure or is drawn from the external environment.

Key Terms

- **halophile**: An organism that lives and thrives in an environment of high salinity, often requiring such an environment; a form of extremophile.

Crenarchaeota can be extreme halophiles, and include organisms living in highly salty environments (for example, halococcus).

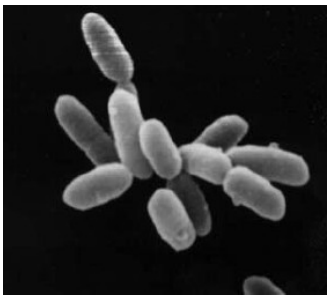

Figure: **Archaea**: Cluster of halobacterium (archaea)

Halococcus is a genus of extremely halophilic archaea, meaning that they require high salt levels, sometimes as high as 32% NaCl, for optimal growth. Halophiles are found mainly in inland bodies of water with high salinity, where their pigments (from a protein called rhodopsinprotein) tint the sediment bright colors. Rhodopsin protein and other proteins serve to protect Halococcus from the extreme salinities of the environment. Some Halococcus may be located in highly salted soil or foods. Because they can function under such high-salt conditions, Halococcus and similar halophilic organisms have been utilized economically in the food industry and even in skin-care production. Halococcus' genome has not been sequenced yet, although studies of its 16s rDNA have demonstrated its placement on the phylogenetic tree. Due to the organisms' potential longevity, Halococcus may be a good candidate for exploring taxonomic similarities to life found in outer space.

Halococcus is able to survive in its high-saline habitat by preventing the dehydration of its cytoplasm. To do this they use a solute, which is either found in their cell structure or is drawn from the external environment. Special chlorine pumps allow the organisms to retain chloride to maintain osmotic balance with the salinity of their habitat. The cells are cocci, 0.6-1.5 micrometres long, with sulfated polysaccharide walls. The cells are organtrophic, using amino acids, organic acids, or carbohydrates for energy. In some cases they are also able to photosynthesize.

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8.14E: Psychrophilic Crenarchaeota

Psychrophiles crenarchaeotes are extremophilic organisms that are capable of growth and reproduction in cold temperatures.

Learning Objectives

- Discuss the specific characteristics associated with psychrophilic crenarchaeotes

Key Points

- Psychrophiles are characterized by lipid cell membranes chemically resistant to the stiffening caused by extreme cold, and often create protein 'antifreezes' to keep their internal space liquid and protect their DNA even in temperatures below water's freezing point.
- Crenarchaea are thought to be very abundant and one of the main contributors to the fixation of carbon.
- Crenarchaeote are abundant in the ocean and some species have a 200 times greater affinity for ammonia than ammonia oxidizing bacteria, leading researchers to challenge the previous belief that ammonia oxidizing bacteria are primarily responsible for nitrification in the ocean.

Key Terms

- **crenarchaeota**: Archae that have been recently identified to be present in marine environments where they responsible for nitrification.
- **psychrophile**: An organism that can live and thrive at temperatures much lower than normal; a form of extremophile.

Psychrophiles or cryophiles (adj. cryophilic) are extremophilic organisms that are capable of growth and reproduction in cold temperatures, ranging from −15°C to +10°C. Temperatures as low as −15°C are found in pockets of very salty water (brine) surrounded by sea ice. They can be contrasted with thermophiles, which thrive at unusually hot temperatures. The environments they inhabit are ubiquitous on Earth, as a large fraction of our planetary surface experiences temperatures lower than 15°C. They are present in alpine and arctic soils, high-latitude and deep ocean waters, polar ice, glaciers, and snowfields. Most psychrophiles are bacteria or archaea, and psychrophily is present in widely diverse microbial lineages within those broad groups. Psychrophiles are characterized by lipid cell membranes chemically resistant to the stiffening caused by extreme cold, and often create protein 'antifreezes' to keep their internal space liquid and protect their DNA even in temperatures below water's freezing point.

The Crenarchaeota (Greek for "spring old quality") (also known as Crenarchaea or eocytes) are Archaea that have been classified as either a phylum of the Archaea kingdom or a kingdom of its own. Initially, the Crenarchaeota were thought to be sulfur-dependent extremophiles but recent studies have identified characteristic Crenarchaeota environmental rRNA indicating the organism may be the most abundant archaea in the marine environment. Originally, they were separated from the other archaea based on rRNA sequences. However, other physiological features, such as lack of histones have supported this division, although some crenarchaea were found to have histones. Until recently all cultured Crenarchaea had been thermophilic or hyperthermophilic organisms, some of which have the ability to grow at up to 113 °C. These organisms stain Gram negative and are morphologically diverse having rod, cocci, filamentous and oddly shaped cells. Beginning in 1992, data were published that reported sequences of genes belonging to the Crenarchaea in marine environments making these bacteria psychrophiles or cryophiles. Since then, analysis of the abundant lipids from the membranes of Crenarchaea taken from the open ocean have been used to determine the concentration of these "low temperature Crenarchaea." Based on these measurements of their signature lipids, Crenarchaea are thought to be very abundant and one of the main contributors to the fixation of carbon. DNA sequences from Crenarchaea have also been found in soil and freshwater environments, suggesting that this phylum is ubiquitous to most environments.

Nitrification, as stated above, is formally a two-step process; in the first step ammonia is oxidized to nitrite, and in the second step nitrite is oxidized to nitrate. Different microbes are responsible for each step in the marine environment. Several groups of ammonia oxidizing bacteria (AOB) are known in the marine environment, including Nitrosomonas, Nitrospira, and Nitrosococcus. All contain the functional gene ammonia monooxygenase (AMO) which, as its name implies, is responsible for the oxidation of ammonia. More recent metagenomic studies have revealed that some Crenarchaeote Archaea possess AMO. Crenarchaeote are abundant in the ocean and some species have a 200 times greater affinity for ammonia than AOB, leading researchers to challenge the previous belief that AOB are primarily responsible for nitrification in the ocean.

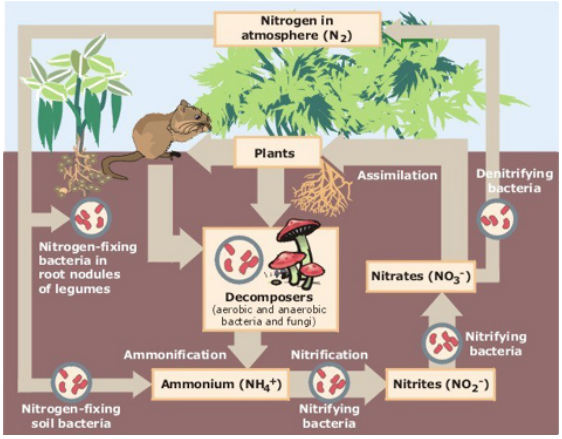

Figure: **Nitrogen Cycling**: Nitrification is the biological oxidation of ammonia with oxygen into nitrite followed by the oxidation of these nitrites into nitrates. Degradation of ammonia to nitrite is usually the rate limiting step of nitrification. Nitrification is an important step in the nitrogen cycle in soil.

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SECTION OVERVIEW

8.15: Euryarchaeota

Topic hierarchy

8.15A: Diverse Cell Forms of Methanogens

8.15B: Extremely Halophilic Archaea

8.15C: Methane-Producing Archaea - Methanogens

8.15D: Thermoplasmatales, Thermocaccales, and Methanopyrus

8.15E: Archaeoglobus

8.15F: Nanoarchaeum and Aciduliprofundum

8.15G: Hyperthermophilic Archaea, H_2, and Microbial Evolution

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8.15A: Diverse Cell Forms of Methanogens

Diverse Cell Forms of Methanogens

There are over 50 described species of methanogens, sharing over 30 signature proteins.

LEARNING OBJECTIVES

Outline the physical characteristics associated with methanogens

KEY TAKEAWAYS

Key Points

- Methanogens are usually either coccoid (spherical) or bacilli (rod shaped).
- Methanogens have a cell wall that is composed of pseudopeptidoglycan, which offers lysozyme resistance.
- There are many diverse strains of methanogens, including *M. smithii* (found in the human gut), *M. kandleri* (discovered on the wall of a black smoker), and *M acetivorans* (found in oil wells, trash dumps, and deep-sea hydrothermal vents).

Key Terms

- **polysaccharide**: Complex sugars. A polymer made of many saccharide units linked by glycosidic bonds.

Methanogens belong to the domain archaea, which are distinctly different than bacteria. There are over 50 described species of methanogens, sharing over 30 signature proteins. These species do not form a monophyletic group, but are split into three clades. Therefore, the large numbers of proteins uniquely shared by all methanogens may be due to lateral gene transfers.



Figure: **Methanopyrus kandleri**: M. kandleri, a methanogen, is the only strain in the genus Methanopyrus. Methanopyrus kandleri can survive and reproduce at 122°C.

Methanogens are usually either coccoid (spherical) or bacilli (rod shaped). The cell walls of of Methanogens, like other Archaea, lack peptidoglycan, a polymer found in the cell walls of the bacteria. Instead, some methanogens have a cell wall that is composed of pseudopeptidoglycan. Pseudopeptidoglycan differs in chemical structure from bacterial peptidoglycan, but resembles eubacterial peptidoglycan in morphology, function, and physical structure. These differences makes these archaea resistant to the enzyme, lysozyme, which only breaks down β (1,4) sugar linkages like those found in peptidoglycan. Those that do not contain pseudopeptidoglycan have at least one paracrystalline array (S-layer) made up of proteins that fit together like a jigsaw puzzle.

There are many diverse strains of methanogens. Methanobrevibacter smithii is the dominant archaeon in the human gut. M. smithii is pivotal in the removal of excess hydrogen from the human gut. They are important for the efficient digestion of polysaccharides, allowing for an increase in the transformation of nutrients into calories.

Methanocaldococcus jannaschii thermophilic methanogen isolated from a hot spring at Woods hole. It was the first archaeon to have its complete genome sequenced, identifying many genes and synthesis pathways unique to the archaea.

Methanopyrus is a genus of methanogens, with a single described species, M. kandleri. M. kandleri is a hyperthermophile, discovered on the wall of a black smoker from the Gulf of California at a depth of 2000 m, at temperatures of 84-110 °C.

Methanosarcina acetivorans is a versatile methane producing microbe which is found in such diverse environments as oil wells, trash dumps, deep-sea hydrothermal vents, and oxygen-depleted sediments beneath kelp beds. Only M. acetivorans and microbes in the genus Methanosarcina use all three known metabolic pathways for methanogenesis.

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8.15B: Extremely Halophilic Archaea

Halophiles are extremophiles that thrive in environments with very high concentrations of salt.

Learning Objectives

- Describe the methods employed by halophilic Archaea to prevent water loss

Key Points

- Halophiles can be found anywhere with a salt concentration at least five times greater than that of the ocean.
- Most halophilic organisms cope with the high concentrations of salt by expending energy to exclude salt from their cytoplasm.
- Halophiles prevent this loss of water by increasing the internal osmolarity of the cell by accumulating osmoprotectants or by the selective uptake of potassium ions.

Key Terms

- **halotolerance**: The adaptation of a living organism to conditions of high salinity (dissolved salt).
- **zwitterionic**: Pertaining to a neutral molecule containing both positive and negative charge.
- **osmoprotectant**: Any osmolyte that helps an organism to survive osmotic stress

Halophiles are extremophiles that thrive in environments with very high concentrations of salt. In fact, the very name “halophile” comes from the Greek word for “salt-loving. ” Although some halophilic bacteria and eukaryotes exist, the largest classification of halophiles is in the Archaea domain.

Halophiles can be found anywhere with a salt concentration at least five times greater than that of the ocean. They are categorized as slight, moderate, or extreme halophiles based on the extent of their halotolerance. Halophiles thrive in places such as the Great Salt Lake, Owens Lake in California, evaporation ponds, and the Dead Sea – places that provide an inhospitable environment to most lifeforms.



Figure: **Dead Sea**: Salt builds up along the Dead Sea. These extreme conditions provides an inhospitable environment to most life forms.

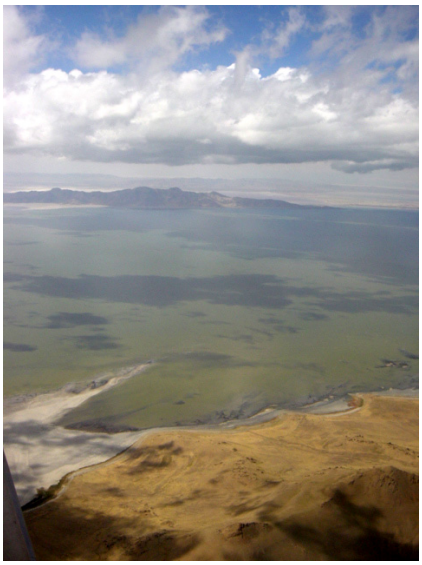

Figure: **Great Salt Lake**: Halophiles are adapted to conditions of extreme salt concentration, such as the Great Salt Lake in Utah.

High salinity represents an extreme environment that relatively few organisms have been able to adapt to and occupy. Most halophilic organisms cope with the high concentrations of salt by expending energy to exclude salt from their cytoplasm to avoid protein aggregation, or "salting out. " "Normal" organisms would desiccate in these conditions, losing water via osmosis out of the cytoplasm. Halophiles prevent this loss of water by increasing the internal osmolarity of the cell. One way halophilic archaea can increase their internal osmolarity is by accumulating organic compounds – called osmoprotectants – in their cytoplasm. These compatible solutes can be accumulated from the environment or synthesized. The most common compatible solutes are neutral or zwitterionic, and include amino acids, sugars, polyols, betaines and ectoines, as well as derivatives of some of these compounds.

A more radical adaptation to preventing water loss employs the selective influx of potassium (K^+) ions into the cytoplasm. In archaea, this adaptation is restricted to the the extremely halophilic family Haloarchaea (often known as Halobacteriaceae). To use this method, the entire intracellular machinery – including enzymes, structural proteins, and charged amino acids that allow the retention of water molecules on their surfaces – must be adapted to high salt levels. In the compatible solute adaptation, little or no adjustment is required of intracellular macromolecules – in fact, the compatible solutes often act as general stress protectants as well as osmoprotectants.

The extremely halophilic Haloarchaea require at least a 2 M salt concentration and are usually found in saturated solutions (about 36% w/v salts). These are the primary inhabitants of salt lakes, inland seas, and evaporating ponds of seawater. The red color of deep salterns is due to the carotenoids (organic pigment) in these archaea. These archaea require salt for growth and they will lyse if they are exposed to less salty environment.

The high concentration of NaCl in halophilic environment limits the availability of oxygen for respiration. Halophiles are chemoheterotrophs, using light for energy and methane as a carbon source under aerobic or anaerobic conditions.

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8.15C: Methane-Producing Archaea - Methanogens

Methanogens are an important group of microoraganisms that produce methane as a metabolic byproduct under anaerobic conditions.

Learning Objectives

- Discuss the characteristics associated with methane-producing archaea

Key Points

- Methanogens are responsible for the methane in the belches of ruminants and in the flatulence in humans.
- Methanogens play a vital ecological role in anaerobic environments by removing excess hydrogen and fermentation products produced by other forms of anaerobic respiration.
- Methanogens play a key role in the remineralization of organic carbon and under the right conditions can form reservoirs of methanogen, a potent greenhouse gas.

Key Terms

- **extremophiles**: An extremophile (from Latin extremus, meaning “extreme,” and Greek philiā (φ), meaning “love”) is an organism that thrives in physically or geochemically extreme conditions that are detrimental to most life on earth.

Methanogenic archaea, or methanogens, are an important group of microoraganisms that produce methane as a metabolic byproduct under anaerobic conditions. Methanogens belong to the domain archaea, which is distinct from bacteria. Methanogens are commonly found in the guts of animals, deep layers of marine sediment, hydrothermal vents, and wetlands. They are responsible for the methane in the belches of ruminants, as in, the flatulence in humans, and the marsh gas of wetlands. Methanogens should not be confused with methanotrophs, which consume methane rather than produce it.



Figure: **Methane**: The flatulence of cows is only a small portion of cows’ methane release. Cows also burp methane due to methanogens in their digestive systems.

Methanogens play a vital ecological role in anaerobic environments by removing excess hydrogen and fermentation products produced by other forms of anaerobic respiration. Because of this, methanogens thrive in environments in which all electron acceptors other than CO2 (such as oxygen, nitrate, trivalent iron, and sulfate) have been depleted.

In the human gut, accumulation of hydrogen reduces the efficiency of microbial processes, reducing energy yield. Methanogens such as *M. smithii* are pivotal in the removal of this excess hydrogen from the gut and may be useful therapeutic targets for reducing energy harvest in obese humans.

In marine sediments, biomethanation is generally confined to where sulfates are depleted, below the top layers. Methanogens play a key role in the remineralization of organic carbon in continental margin sediments and other aquatic sediments with high rates of sedimentation and organic matter. Under the correct temperatures and pressure, biogenic methane can accumulate in massive deposits, which account for significant fractions of organic carbon and key reservoirs of a potent greenhouse gas.

Some methanogens, called extremophiles, can thrive in extreme environments such as hot springs, submarine hydrothermal vents, and hot, dry deserts. Methanogens have been found buried under kilometers of ice in Greenland, as well as in the “solid” rock of the Earth’s crust, kilometers below the surface.

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8.15D: Thermoplasmatales, Thermocaccales, and Methanopyrus

There are many classes in the phylum Euryarchaeota, many of which are extremophiles.

Learning Objectives

- Recognize the characteristics associated with the Euryarchaeota classes of thermophiles: Thermoplasmatales, Thermococcales and Methanopyri

Key Points

- Thermoplasmatales are an order of the class Thermoplasmata. All are acidophiles, growing optimally at pH below 2.
- Another anaerobic Euryarchaeota, often hyperthermophiles, are the Thermococcales of the class Thermococococci.
- Methanopyrus is a genus of methanogen, with a single described species, M. kandleri.

Key Terms

- **acidophiles**: an organism that thrives under highly acidic conditions (usually at pH 2.0 or below)
- **hyperthermophile**: An organism that lives and thrives in an extremely hot environment like a deep sea smoker vent; often a member of the Archaea.

There are many classes in the phylum Euryarchaeota, many of which are extremophiles, surviving in extreme conditions that are uninhabitable for most other organisms. Thermoplasmatales, Thermococcales, and Methanopyri are all Euryarchaeota Classes of thermophiles.

Thermoplasmatales are an order of the class Thermoplasmata. All are acidophiles, growing optimally at pH below 2. Picrophilus is currently the most acidophilic of all known organisms growing at a minimum pH of 0.06. Many of these organisms do not contain a cell wall, although this is not true in the case of Picrophilus. Most members of the Thermotoplasmata are thermophilic. A thermophile is an extremophile that thrives at relatively high temperatures, between 45 and 122 °C. Many of them are archaea. Thermophilic eubacteria are suggested to have been among the earliest bacteria. Thermophiles contain enzymes that can function at high temperatures, and can even survive at much higher temperatures, whereas other bacteria would be damaged and sometimes killed if exposed to the same temperatures.

Another anaerobic Euryarchaeota, often hyperthermophiles, are the Thermococcales of the class Thermococococci.

Methanopyrus is a genus of methanogen, with a single described species, *Methanopyrus kandleri* . It is a hyperthermophile, discovered on the wall of a black smoker from the Gulf of California at a depth of 2000 m, at temperatures of 84-110 °C. Strain 116 was discovered in black smoker fluid of the Kairei hydrothermal field; it can survive and reproduce at 122 °C. It lives in a hydrogen-carbon dioxide rich environment, and like other methanogens reduces the latter to methane. It is placed among the Euryarchaeota, in its own class, Methanopyri.

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8.15E: Archaeoglobus

Archaeoglobus is a genus of Euryarchaeota found in high-temperature oil fields.

Learning Objectives

- Outline the unique traits associated with Archaeoglobus

Key Points

- Archaeoglobus are sulfate-reducing archaea, coupling the reduction of sulfate to sulfide with the oxidation of many different organic carbon sources, including complex polymers.
- Archaeoglobus grow at extremely high temperatures and are found in hydrothermal vents, oil deposits, and hot springs.
- Comparative genomic studies on archaeal genomes provide evidence that members of the genus Archaeoglobus are the closest relatives of methanogenic archaea.

Key Terms

- **lithoautotroph**: A microbe that takes energy from reduced compounds of minerals.
- **heterotroph**: An organism that requires an external supply of energy in the form of food as it cannot synthesize its own.
- **hyperthermophiles**: An organism that thrives in extremely hot environments-from 60 degrees C (140 degrees F) upwards.

Archaeoglobus is a genus of Euryarchaeota found in high-temperature oil fields, where they may contribute to oil field souring. Archaeoglobus are sulfate-reducing archaea, coupling the reduction of sulfate to sulfide with the oxidation of many different organic carbon sources, including complex polymers.

Archaeoglobus grow at extremely high temperatures between 60 and 95 °C, with optimal growth at 83 °C. These hyperthermophiles can be found in hydrothermal vents, oil deposits, and hot springs. They can produce biofilm to form a protective environment when subjected to environmental stresses such as extreme pH or temperature, high concentrations of metal, or the addition of antibiotics, xenobiotics, or oxygen. These archaeons are known to cause the corrosion of iron and steel in oil and gas processing systems by producing iron sulphide. Their bioflims, however, may have industrial or research applications in the detoxification of metal contaminated samples or to gather metals in an economically recoverable form.

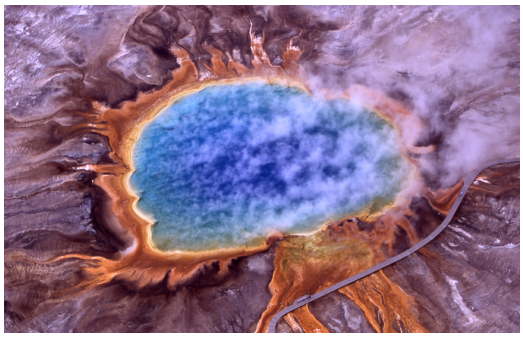

Figure: **Microbial Mats Around the Grand Prismatic Spring**: Thermophiles produce some of the bright colors of Grand Prismatic Spring, Yellowstone National Park

Archaeoglobus are lithotrophs, and can be either autotrophic or heterotrophic.The archaeoglobus strain *A. lithotrophicus* are lithoautotrophs, and derive their energy from hydrogen, sulfate and carbon dioxide. The strain *A. profundus* are also lithotrophic, but as they require acetate and CO2 for biosynthesis, and are therefore heterotrophs. Archaeoglobus species utilize their environment by acting as scavengers with many potential carbon sources. They can obtain carbon from fatty acids, the degradation of amino acids, aldehydes, organic acids, and possibly carbon monoxide (CO) as well.

Comparative genomic studies on archaeal genomes provide evidence that members of the genus Archaeoglobus are the closest relatives of methanogenic archaea. This is supported by the presence of 10 conserved signature proteins that are uniquely found in all methanogens and Archaeoglobus. Additionally, 18 proteins which are uniquely found in members of Thermococci, Archaeoglobus and methanogens have been identified, suggesting that these three groups of Archaea may have shared a common relative exclusive of other Archaea. However, the possibility that the shared presence of these signature proteins in these archaeal lineages is due to lateral gene transfer cannot be excluded.

The complete genome sequence from *Archaeoglobus fulgidus* reveals the presence of a complete set of genes for methanogenesis. The function of these genes in *A. fulgidus* remains unknown, and the lack of the enzyme methyl-CoM reductase does not allow for methanogenesis to occur by a mechanism similar to that found in other methanogens.

The *A. fulgidus* genome is a circular chromosome of 2,178,000 base pairs, roughly half the size of *E. coli*. A quarter of the genome encodes preserved proteins whose functions are not yet determined, but are expressed in other archaeons such as *Methanococcus jannaschii*. Another quarter encodes proteins unique to the archaeal domain. One observation about the genome is that there are many gene duplications and the duplicated proteins are not identical. This suggests metabolic differentiation specifically with respect to the decomposing and recycling carbon pathways through scavenged fatty acids. The duplicated genes also gives the genome a larger genome size than its fellow archaeon *M. jannaschii*.

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8.15F: Nanoarchaeum and Aciduliprofundum

Nanoarchaeum equitans is a species of marine Archaea discovered in a hydrothermal vent off the coast of Iceland.

Learning Objectives

- Discuss the unique characteristics associated with Nanoarchaeum

Key Points

- Nanoarchaeum grows best in environments with a pH of six and a salinity concentration of 2%.
- Nanoarchaeum cannot synthesize lipids but obtains them from its host, Ignicoccus.
- The genome and proteome composition of N. equitans are marked with the signatures of dual adaptation – one to high temperature and the other to obligatory parasitism.

Key Terms

- **nanobes**: A tiny filamental structure that may or not be a living organism, and if living, would be the smallest form of life, 1/10 the size of the smallest known bacteria.

Nanoarchaeum equitans is a species of marine Archaea that was discovered in 2002 in a hydrothermal vent off the coast of Iceland on the Kolbeinsey Ridge by Karl Stetter. Strains of this microbe were also found on the Sub-polar Mid Oceanic Ridge and in the Obsidian Pool in Yellowstone National Park. It is a thermophile that grows in temperatures approaching boiling (80 degrees Celsius). Nanoarchaeum grows best in environments with a pH of six, and a salinity concentration of 2%. Nanoarchaeum cannot synthesize lipids but obtains them from its host, Ignicoccus. Nanoarchaeum appears to be an obligatory symbiont of this archaeon Ignicoccus, and must be in contact with it to survive.



Figure: **Nanoarchaeum equitans**: Image of Nanoarchaeum equitans (and its host Ignicoccus).

Nanoarchaeum cells are only 400 nm in diameter, making it the next smallest known living organism to nanobacteria and nanobes, whose status as living organisms is controversial. Its genome is only 490,885 nucleotides long; the smallest non-viral genome ever sequenced next to that of Candidatus Carsonella ruddii. N. equitans genome consists of a single circular chromosome, and lacks almost all genes required for synthesis of amino acids, nucleotides, cofactors, and lipids, but encodes everything needed for repair and replication. 95% of its DNA encodes for proteins for stable RNA molecules. Nanoarchaeum has small appendages that come out of its circular structure. The cell surface is covered by a thin, lattice-shaped S-layer, which provides structure and protection for the entire cell. Genetically, Nanoarchaeum is peculiar in that its 16S RNA sequence is undetectable by the most common methods.

The sequencing of the Nanoarchaeum genome has revealed a wealth of information about the organism's biology. The genes for several vital metabolic pathways appear to be missing. Nanoarchaeum cannot synthesize most nucleotides, amino acids, lipids, and cofactors. The cell most likely obtains these biomolecules from Ignicoccus. However, unlike many parasitic microbes, Nanoarchaeum has many DNA repair enzymes, as well as everything necessary to carry out DNA replication, transcription, and translation. This may explain why the genome lacks the large stretches of non-coding DNA characteristic of other parasites. The organism's ability to produce its own ATP is also in question. Nanoarchaeum lacks the ability to metabolize hydrogen and sulfur for energy, as many thermophiles do. It does have five subunits of an ATP synthase as well as pathways for oxidative deamination. Whether it obtains energy from biological molecules imported from Ignicoccus, or whether it receives ATP directly is currently unknown. The genome and proteome composition of N. equitans are marked with the signatures of dual adaptation – one to high temperature and the other to obligatory parasitism (or symbiosis).

Aciduliprofundum is another genus of the Euryarchaeota, though relatively less is known about it.

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8.15G: Hyperthermophilic Archaea, H_2, and Microbial Evolution

A hyperthermophile is an organism that thrives in extremely hot environments, from 60 degrees C (140 degrees F) and up.

Learning Objectives

- Discuss the characteristics associated with hyperthermophiles

Key Points

- Many hyperthermophiles are also able to withstand other environmental extremes like high acidity or radiation levels.
- The current record growth temperature is 122°C for Methanopyrus kandleri.
- Although no hyperthermophile has yet been discovered living at temperatures above 122°C, their existence is very possible.
- It is thought unlikely that microbes could survive at temperatures above 150°C, as the cohesion of DNA and other vital molecules begins to break down at this point.
- The protein molecules in hyperthermophiles exhibit hyperthermostability and can maintain structural stability (and therefore function) to adapt to high temperatures.

Key Terms

- **hyperthermophile**: An organism that lives and thrives in an extremely hot environment like a deep sea smoker vent; often a member of the Archaea.

A hyperthermophile is an organism that thrives in extremely hot environments, from 60 degrees C (140 degrees F) and up. Hyperthermophiles are a subset of extremophiles within the domain Archaea. An optimal temperature for the existence of hyperthermophiles is above 80°C (176°F). Some bacteria are even able to tolerate temperatures of around 100°C (212°F). Many hyperthermophiles are also able to withstand other environmental extremes like high acidity or radiation levels.

Hyperthermophiles were first discovered by Thomas D. Brock in hot springs in Yellowstone National Park, Wyoming. Since then, more than 70 species have been discovered. The most hardy hyperthermophiles yet discovered live on the superheated walls of deep-sea hydrothermal vents, requiring temperatures of at least 90°C for survival.

One extraordinary heat-tolerant hyperthermophile is the recently discovered Strain 121, an archaeon living at 121°C in the Pacific Ocean. Strain 121 has been able to double its population during 24 hours in an autoclave at 121°C (hence its name). Strain 121 survived being heated to 130°C for two hours, but was unable to reproduce until it was transferred to fresh growth medium at the relatively cooler temperature of 103°C. The current record growth temperature is 122°C for *Methanopyrus kandleri* ,an archaeon found in a Central Indian Ridge. Other hyperthermophile archaea include *Pyrolobus fumarii*, which lives at 113°C in Atlantic hydrothermal vents, and *Pyrococcus furiosus*, first discovered in Italy near a volcanic vent.

Although no hyperthermophile has yet been discovered living at temperatures above 122°C, their existence is very possible. However, it is thought unlikely that microbes could survive at temperatures above 150°C, as the cohesion of DNA and other vital molecules begins to break down at this point.

There are a number of proposed high temperature adaptions of hyperthermophiles. Early research into hyperthermophiles speculated that their genome could be characterized by high guanine-cytosine content; however, recent studies show that there is no obvious correlation between the GC content of the genome and the optimal environmental growth temperature of the organism. The protein molecules in the hyperthermophiles exhibit hyperthermostability – that is, they can maintain structural stability (and therefore function) at high temperatures. Such proteins are homologous to their functional analogues in organisms which thrive at lower temperatures, but have evolved to exhibit optimal function at much greater temperatures. Most of the low-temperature homologues of the hyperthermostable proteins would be denatured above 60°C. Such hyperthermostable proteins are often commercially important, as chemical reactions proceed faster at high temperatures. The cell membrane of hyperthermophiles contains high levels of saturated fatty acids, which are usually arranged in a C40 monolayer to retain its shape at high temperatures.

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SECTION OVERVIEW

8.16: Eukaryotic Microbial Diversity

Topic hierarchy

8.16A: Phylogeny of the Eukarya

8.16B: Historical Overview of Eukaryotes

8.16C: Opisthokonts - Animals and Fungi

8.16D: Endosymbiotic Theory and the Evolution of Eukaryotes

8.16E: Cell Structure, Metabolism, and Motility

8.16F: Newly Discovered Eukaryotes

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8.16A: Phylogeny of the Eukarya

Eukaryotes are very diverse in phylogenic terms, the common feature being a membrane bound nucleus.

Learning Objectives

- Assess the phylogeny of Eukarya

Key Points

- Eukaryotes are broadly determined by the prescence of a membrane bound nucleus, though many eukaryotes have other membrane bound structures.
- The domain of eukarya are broadly grouped into six kingdoms: Excavata, Amoebozoa, Opisthokonta, Rhizaria, Chromalveolata, and Archaeplastida.
- The exact nature of the relationships (i.e. common ancestors) of the the eukarya domain are still debated.

Key Terms

- **crown group**: In phylogenetics, the crown group of a collection of species consists of the living representatives of the collection together with their ancestors back to their last common ancestor as well as all of that ancestor's descendants. It is thus a clade, a group consisting of a species and all its descendents.
- **cristae**: Cristae (singular crista) are the internal compartments formed by the inner membrane of a mitochondrion. They are studded with proteins, including ATP synthase and a variety of cytochromes.

Phylogeny of the Eukarya

A eukaryote is an organism whose cells contain complex structures enclosed within membranes. Eukaryotes may more formally be referred to as the taxon Eukarya or Eukaryota. The defining membrane-bound structure that sets eukaryotic cells apart from prokaryotic cells is the nucleus, or nuclear envelope, within which the genetic material is carried. Most eukaryotic cells also contain other membrane-bound organelles such as mitochondria, chloroplasts, and the Golgi apparatus. All large complex organisms are eukaryotes, including animals, plants, and fungi. The group also includes many unicellular organisms.

rRNA trees constructed during the 1980s and 1990s left most eukaryotes in an unresolved crown group, which was usually divided by the form of the mitochondrial cristae. The few groups that lack mitochondria branched separately, and so the absence was believed to be primitive. But this is now considered an artifact of a divergent evolutionary line, and they are known to have lost them secondarily.

Eukaryotes are split into 6, subdivisions, referred to as kingdoms. They include:

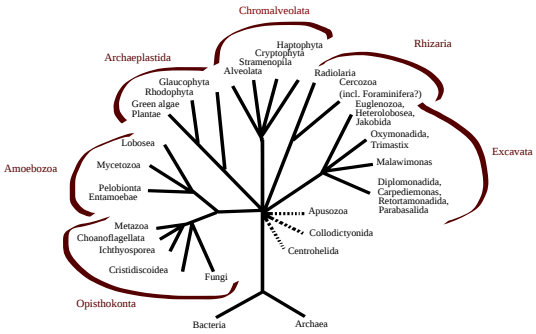

Figure: **The Six Kingdoms**: This is one hypothesis of eukaryotic relationships. The Opisthokonta group includes both animals (Metazoa) and fungi. Plants (Plantae) are placed in Archaeplastida.

1. Excavata – Various flagellate protozoa

2. Amoebozoa – Most lobose amoeboids and slime moulds

3. Opisthokonta – Animals, fungi, choanoflagellates

4. RhizariaForaminifera – Radiolaria, and various other amoeboid protozoa

5. ChromalveolataStramenopiles (or Heterokonta) – Haptophyta, Cryptophyta (or cryptomonads), and Alveolata

6. Archaeplastida (or Primoplantae) – Land plants, green algae, red algae, and glaucophytes

There is widespread agreement that the Rhizaria belong with the Stramenopiles and the Alveolata, in a clade dubbed the SAR supergroup, so that Rhizara is not one of the main eukaryote groups. The Amoeboza and Opisthokonta are each monophyletic and form a clade, often called the unikonts. There is debate about the true constituents of the animal kingdoms.

Beyond this, there does not appear to be a consensus. It has been estimated that there may be 75 distinct lineages of eukaryotes. Most of these lineages are protists. The known eukaryote genome sizes vary from 8.2 megabases (Mb) in Babesia bovis to 112,000 to 220,050 Mb in the dinoflagellate Prorocentrum micans. This suggests that the genome of the ancestral eukaryote has undergone considerable variation during its evolution. The last common ancestor of all eukaryotes is believed to have been a phagotrophic protist with a nucleus, at least one centriole and cilium, facultatively aerobic mitochondria, sex (meiosis), a dormant cyst with a cell wall of chitin, cellulose, and peroxisomes. Later endosymbiosis led to the spread of plastids in some lineages.

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8.16B: Historical Overview of Eukaryotes

Until more recent work, the historical view of eukaryotes has been anthropomorphic.

LEARNING OBJECTIVES

Examine the historical view of eukaryotes

KEY TAKEAWAYS

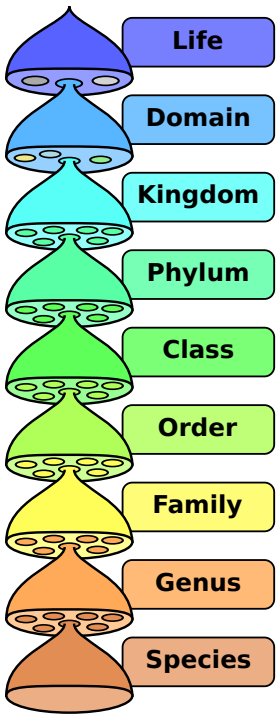
Key Points

- Plants and animals since ancient times have been considered to be related.
- Initially, microscopic organisms were classified into plants or animals.
- Genomic sequencing has reorganized our understanding of life, and how different eukaryotic clades are related.

Key Terms

- **kingdom**: A rank in the classification of organisms, below domain and above phylum; a taxon at that rank (e.g. the plant kingdom, the animal kingdom).
- **clade**: A group of animals or other organisms derived from a common ancestor species.

Even back to Antiquity the two clades of animals and plants were recognized. They were given the taxonomic rank of Kingdom (biology) by Linnaeus. Although he included the fungi with plants with some reservations, it was later realized that they are quite distinct and warrant a separate kingdom, the composition of which was not entirely clear until the 1980's. The various single-cell eukaryotes were originally placed with plants or animals when they became known. The German biologist Georg A. Goldfuss coined the word protozoa in 1830 to refer to organisms such as ciliates and corals. This group was expanded until it encompassed all single-cell eukaryotes. They were given their own kingdom, the Protista, by Ernst Haeckel in 1866.



Biological classification: The hierarchy of biological classification's eight major taxonomic ranks. A genus contains one or more species. Intermediate minor rankings are not shown.

The eukaryotes came to be composed of four kingdoms: Kingdom Protista, Kingdom Plantae, Kingdom Fungi, and Kingdom Animalia. The protists were understood to be "primitive forms," and thus an evolutionary grade, united by their primitive unicellular nature. The disentanglement of the deep splits in the tree of life only really got going with DNA sequencing, leading to a system of domains rather than kingdoms as top level rank being put forward by Carl Woese, uniting all the eukaryote kingdoms

under the eukaryote domain. As such the tree of life consists of three domains: Archaea, Bacteria, and Eukarya. The arrangement of taxa reflects the fundamental differences in the genomes, a less anthropomorphic “animal-centric” world view. At the same time, work on the protist tree intensified, and is still actively going on today. Several alternative classifications have been forwarded, though there is no consensus in the field.

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8.16C: Opisthokonts - Animals and Fungi

Learning Objectives

- Describe Opistkokonts

The opisthokonts, or “fungi/metazoa group”, are a broad group of eukaryotes, including both the animal and fungus kingdoms, together with the eukaryotic microorganisms that are sometimes grouped in the paraphyletic phylum choanozoa (previously assigned to the protist “kingdom”). Both genetic and ultrastructural studies strongly support that opisthokonts form a monophyletic group.

One common characteristic of opisthokonts is that flagellate cells, such as most animal sperm and chytrid spores, propel themselves with a single posterior flagellum. This gives the group its name. In contrast, flagellate cells in other eukaryote groups propel themselves with one or more anterior flagellae. Most fungi do not produce cells with flagellae, but the primitive fungal chytrids do, suggesting that a common ancestor of current fungal species did have a flagellum.

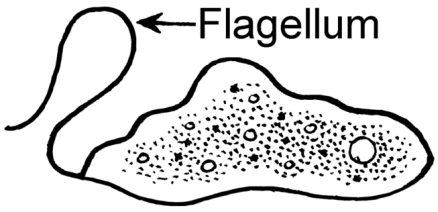

Figure: **Flagellum**: Here is a depiction of a unicellular organism with a flagellum. Flagella are a typical structure found on opisthokonts, sometimes at only specific points of the a life cycle.

The close relationship between animals and fungi was suggested by Cavalier-Smith in 1987, who used the informal name opisthokonta (the formal name has been used for the chytrids). The discovery was confirmed by later genetic studies. Early phylogenies placed opisthokonts near the plants and other groups that have mitochondria with flat cristae, but this character varies. Cavalier-Smith and Stechmann argue that the uniciliate eukaryotes such as opisthokonts and Amoebozoa, collectively called unikonts, split off from the other biciliate eukaryotes, called bikonts, shortly after they evolved.

Opisthokonts are divided into Holomycota or Nucletmycea (fungi and all organisms more closely related to fungi than to animals) and Holozoa (animals and all organisms more closely related to animals than to fungi); no opisthokonts basal to the Holomycota/Holozoa split have yet been identified.

Key Points

- The unifying feature of opisthokonts is the presence of a flagellum, sometimes only ancestrally or at a specific point in the life cycle.
- Genetic sequencing has confirmed that opisthokonts are genetically related.
- Opisthokonts are split into two groups: holomycota (includes fungi), and holozoa (includes animals).

Key Terms

- **monophyletic**: Of, pertaining to, or affecting a single phylum (or other taxon) of organisms.
- **flagellum**: In protists, a long, whiplike membrane-enclosed organelle used for locomotion or feeding.

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8.16D: Endosymbiotic Theory and the Evolution of Eukaryotes

Genome fusion occurs during endosymbiosis, which is the mechanism proposed as responsible for the first eukaryotic cells.

Learning Objectives

- Describe the genome fusion hypothesis and its relationship to the evolution of eukaryotes

Key Points

- Two symbiotic organisms become endosymbiotic when one species is taken inside the cytoplasm of another species, resulting in genome fusion.
- Genome fusion, by endosymbiosis, between two species, one an Archaea and the other a Bacteria, has been proposed as responsible for the evolution of the first eukaryotic cells.
- Gram-negative bacteria are proposed to result from an endosymbiotic fusion of archaeal and bacterial species through a mechanism that has also been used to explain the double membranes found in mitochondria and chloroplasts.
- The nucleus-first hypothesis proposes the nucleus evolved in prokaryotes first, followed by a later fusion of the new eukaryote with bacteria that became mitochondria.
- The mitochondria-first hypothesis proposes mitochondria were first established in a prokaryotic host, which subsequently acquired a nucleus to become the first eukaryotic cell.
- The eukaryote-first hypothesis proposes prokaryotes actually evolved from eukaryotes by losing genes and complexity.

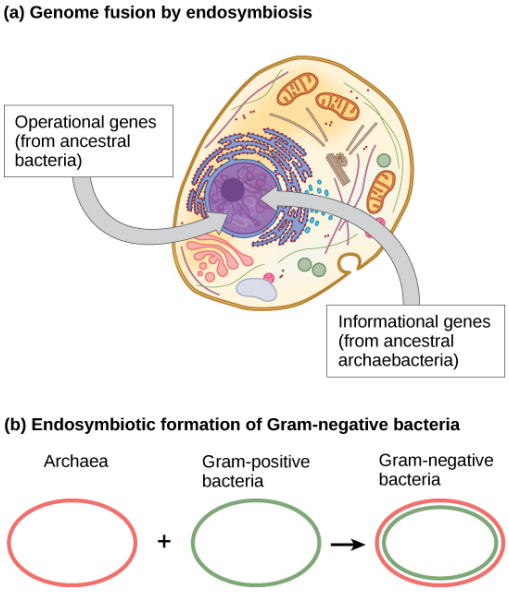
Key Terms

- **genome fusion**: a result of endosymbiosis when a genome consists of genes from both the endosymbiont and the host.
- **symbiotic**: of a relationship with mutual benefit between two individuals or organisms
- **endosymbiosis**: when one symbiotic species is taken inside the cytoplasm of another symbiotic species and both become endosymbiotic

Genome Fusion and the Evolution of Eukaryotes

Scientists believe the ultimate event in HGT (horizontal gene transfer) occurs through genome fusion between different species when two symbiotic organisms become endosymbiotic. This occurs when one species is taken inside the cytoplasm of another species, which ultimately results in a genome consisting of genes from both the endosymbiont and the host. This mechanism is an aspect of the Endosymbiont Theory, which is accepted by a majority of biologists as the mechanism whereby eukaryotic cells obtained their mitochondria and chloroplasts. However, the role of endosymbiosis in the development of the nucleus is more controversial. Nuclear and mitochondrial DNA are thought to be of different (separate) evolutionary origin, with the mitochondrial DNA being derived from the circular genomes of bacteria that were engulfed by ancient prokaryotic cells. Mitochondrial DNA can be regarded as the smallest chromosome. Interestingly enough, mitochondrial DNA is inherited only from the mother. The mitochondrial DNA degrades in sperm when the sperm degrades in the fertilized egg or, in other instances, when the mitochondria located in the flagellum of the sperm fails to enter the egg.

Within the past decade, the process of genome fusion by endosymbiosis has been proposed to be responsible for the evolution of the first eukaryotic cells. Using DNA analysis and a new mathematical algorithm called conditioned reconstruction (CR), it has been proposed that eukaryotic cells developed from an endosymbiotic gene fusion between two species: one an Archaea and the other a Bacteria. As mentioned, some eukaryotic genes resemble those of Archaea, whereas others resemble those from Bacteria. An endosymbiotic fusion event would clearly explain this observation. On the other hand, this work is new and the CR algorithm is relatively unsubstantiated, which causes many scientists to resist this hypothesis.



Endosymbiosis in eukaryotes: The theory that mitochondria and chloroplasts are endosymbiotic in origin is now widely accepted. More controversial is the proposal that (a) the eukaryotic nucleus resulted from the fusion of archaeal and bacterial genomes; and that (b) Gram-negative bacteria, which have two membranes, resulted from the fusion of Archaea and Gram-positive bacteria, each of which has a single membrane.

More recent work proposes that gram-negative bacteria, which are unique within their domain in that they contain two lipid bilayer membranes, did result from an endosymbiotic fusion of archaeal and bacterial species. The double membrane would be a direct result of endosymbiosis, with the endosymbiont picking up the second membrane from the host as it was internalized. This mechanism has also been used to explain the double membranes found in mitochondria and chloroplasts. A lot of skepticism still surrounds this hypothesis; the ideas are still debated within the biological science community.

There are several other competing hypotheses as to the origin of eukaryotes and the nucleus. One idea about how the eukaryotic nucleus evolved is that prokaryotic cells produced an additional membrane which surrounded the bacterial chromosome. Some bacteria have the DNA enclosed by two membranes; however, there is no evidence of a nucleolus or nuclear pores. Other proteobacteria also have membrane-bound chromosomes. If the eukaryotic nucleus evolved this way, we would expect one of the two types of prokaryotes to be more closely-related to eukaryotes. Another hypothesis, the nucleus-first hypothesis, proposes the nucleus evolved in prokaryotes first, followed by a later fusion of the new eukaryote with bacteria that became mitochondria. The mitochondria-first hypothesis, however, proposes mitochondria were first established in a prokaryotic host, which subsequently acquired a nucleus (by fusion or other mechanisms) to become the first eukaryotic cell. Most interestingly, the eukaryote-first hypothesis proposes prokaryotes actually evolved from eukaryotes by losing genes and complexity. All of these hypotheses are testable. Only time and more experimentation will determine which hypothesis is best supported by data.

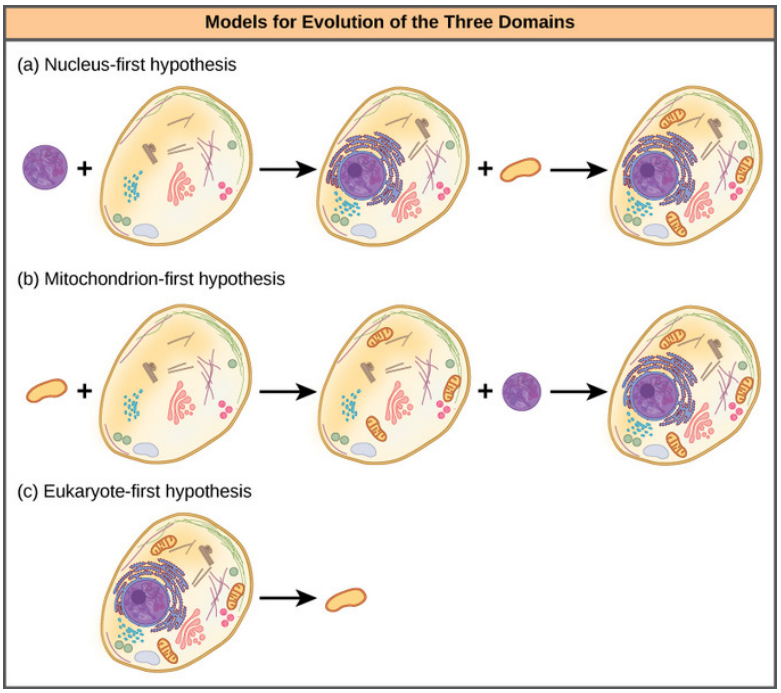


Figure: **Three hypotheses of eukaryotic and prokaryotic evolution**: Three alternate hypotheses of eukaryotic and prokaryotic evolution are (a) the nucleus-first hypothesis, (b) the mitochondrion-first hypothesis, and (c) the eukaryote-first hypothesis.

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8.16E: Cell Structure, Metabolism, and Motility

Protists are an incredibly diverse set of eukaryotes of various sizes, cell structures, metabolisms, and methods of motility.

Learning Objectives

- Describe the metabolism and structure of protists, explaining the structures that provide their motility

Key Points

- Protist cells may contain a single nucleus or many nuclei; they range in size from microscopic to thousands of meters in area.
- Protists may have animal-like cell membranes, plant-like cell walls, or may be covered by a pellicle.
- Some protists are heterotrophs and ingest food by phagocytosis, while other types of protists are photoautotrophs and store energy via photosynthesis.
- Most protists are motile and generate movement with cilia, flagella, or pseudopodia.

Key Terms

- **amorphous**: lacking a definite form or clear shape
- **multinucleate**: having more than one nucleus
- **pellicle**: cuticle, the hard protective outer layer of certain life forms
- **taxis**: the movement of an organism in response to a stimulus; similar to kinesis, but more direct
- **phagocytosis**: the process where a cell incorporates a particle by extending pseudopodia and drawing the particle into a vacuole of its cytoplasm
- **phagosome**: a membrane-bound vacuole within a cell containing foreign material captured by phagocytosis

Cell Structure

The cells of protists are among the most elaborate and diverse of all cells. Most protists are microscopic and unicellular, but some true multicellular forms exist. A few protists live as colonies that behave in some ways as a group of free-living cells and in other ways as a multicellular organism. Still other protists are composed of enormous, multinucleate, single cells that look like amorphous blobs of slime, or in other cases, similar to ferns. Many protist cells are multinucleated; in some species, the nuclei are different sizes and have distinct roles in protist cell function.

Single protist cells range in size from less than a micrometer to thousands of square meters (giant kelp). Animal-like cell membranes or plant-like cell walls envelope protist cells. In other protists, glassy silica-based shells or pellicles of interlocking protein strips encase the cells. The pellicle functions like a flexible coat of armor, preventing the protist from external damage without compromising its range of motion.

Metabolism

Protists exhibit many forms of nutrition and may be aerobic or anaerobic. Protists that store energy by photosynthesis belong to a group of photoautotrophs and are characterized by the presence of chloroplasts. Other protists are heterotrophic and consume organic materials (such as other organisms) to obtain nutrition. Amoebas and some other heterotrophic protist species ingest particles by a process called phagocytosis in which the cell membrane engulfs a food particle and brings it inward, pinching off an intracellular membranous sac, or vesicle, called a food vacuole. The vesicle containing the ingested particle, the phagosome, then fuses with a lysosome containing hydrolytic enzymes to produce a phagolysosome, which breaks down the food particle into small molecules that diffuse into the cytoplasm for use in cellular metabolism. Undigested remains ultimately exit the cell via exocytosis.

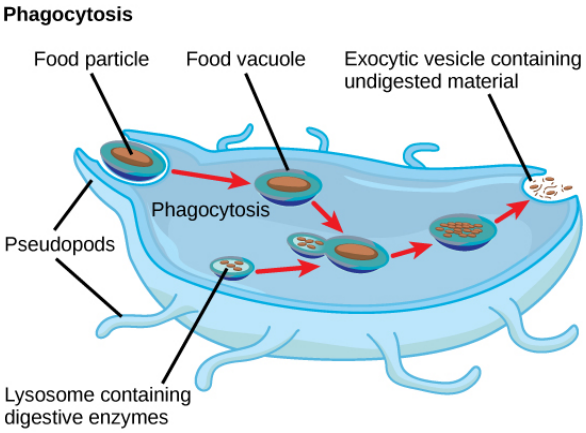

Figure: **Protist metabolism**: The stages of phagocytosis include the engulfment of a food particle, the digestion of the particle using enzymes contained within a lysosome, and the expulsion of undigested materials from the cell.

Subtypes of heterotrophs, called saprobes, absorb nutrients from dead organisms or their organic wastes. Some protists function as mixotrophs, obtaining nutrition by photoautotrophic or heterotrophic routes, depending on whether sunlight or organic nutrients are available.

Motility

The majority of protists are motile, but different types of protists have evolved varied modes of movement. Protists such as euglena have one or more flagella, which they rotate or whip to generate movement. Paramecia are covered in rows of tiny cilia that they beat to swim through liquids. Other protists, such at amoebae, form cytoplasmic extensions called pseudopodia anywhere on the cell, anchor the pseudopodia to a surface, and pull themselves forward. Some protists can move toward or away from a stimulus; a movement referred to as taxis. Protists accomplish phototaxis, movement toward light, by coupling their locomotion strategy with a light-sensing organ.

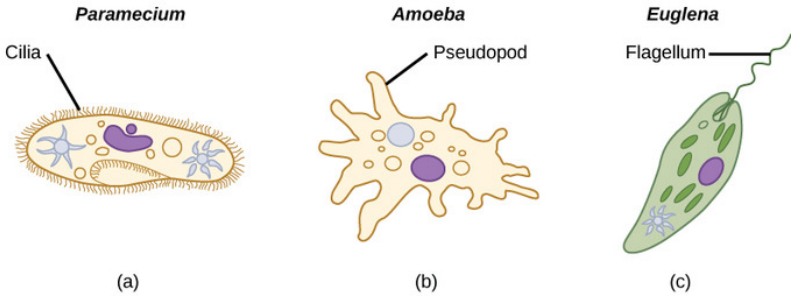

Figure: **Different types of motility in protists**: Protists use various methods for transportation. (a) A paramecium waves hair-like appendages called cilia. (b) An amoeba uses lobe-like pseudopodia to anchor itself to a solid surface and pull itself forward. (c) Euglena uses a whip-like tail called a flagellum.

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8.16F: Newly Discovered Eukaryotes

There are many new species to be discovered, including eukaryotic species.

Learning Objectives

- Recognize Eukaryotic diversity

Key Points

- We know only a fraction of the number of species out there, and most of the attention has been given to large macroscopic species, a true understanding of microscopic eukaryotic life is not known.
- Even though mammals make up a small percentage of the species that are eukaryotes, several new mammalian species have been identified in the last decade.
- As extinction is increasing, we may never know all the eukaryotes that share the world with us.

Key Terms

- **extant**: Still alive; not extinct.
- **metagenomics**: The study of genomes recovered from environmental samples; especially the differentiation of genomes from multiple organisms or individuals, either in a symbiotic relationship, or at a crime scene.

According to the Global Taxonomy Initiative and the European Distributed Institute of Taxonomy, the total number of species for some phyla may be much higher than what was known in 2010:10–30 million insects; (of some 0.9 million we know today) 5–10 million bacteria; 1.5 million fungi; of some 0.075 million we know today. The number of microbial species is not reliably known, but the Global Ocean Sampling Expedition dramatically increased the estimates of genetic diversity by identifying an enormous number of new genes from near-surface plankton samples at various marine locations.

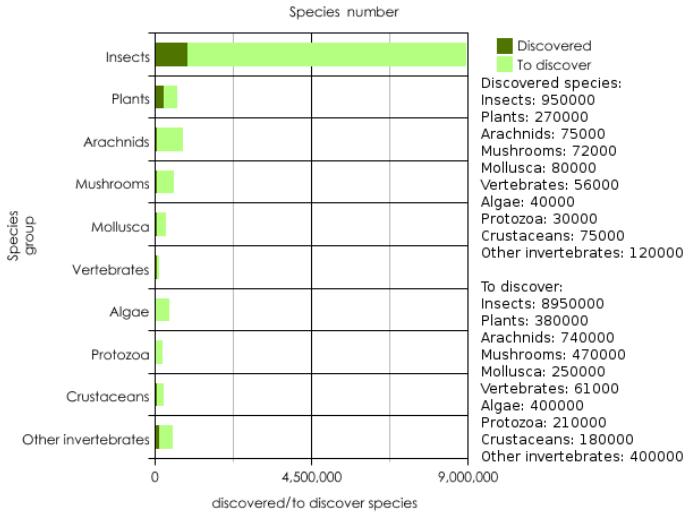

Figure: **Known and Unknown Species**: This graph shows how many species discovered (dark green) versus estimated species remaining to be discovered. This does not include many microscopic eukaryotic groups.

From these studies, it is apparent that less than 1% of all species that have been described have been studied beyond simply noting their existence. The vast majority of Earth's species are microbial. Contemporary biodiversity is "firmly fixated on the visible world". For example, microbial life is metabolically and environmentally more diverse than multicellular life (e.g., extremophile). On the tree of life, based on analyses of small-subunit ribosomal RNA, visible life consists of barely noticeable twigs. The inverse relationship of size and population recurs higher on the evolutionary ladder.

Due to the advent of mass sequencing tools, thousands of new viral species have been identified in metagenomics studies, while at the same time hundreds of new viral species have been found. On top of that, there have been numerous fungal species identified. However, as suggested above most of the attention is given to large species, which represent a very small portion of the new species identified Even with this in mind, since the beginning of this century, 5 marsupial species, 25 primate, 1 elephant, 1 sloth, 3 rabbit, several rodent species, at least 30 new bat species have been discovered. On top of that several subspecies have been found.

Considering how large an elephant is, this should point out how little we know about the numbers of microscopic eukaryotes that are yet to be discovered.

Of course we may never truly identify many eukaryotic species, since the rate of extinction has increased. Many extant species may become extinct before they are described.

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SECTION OVERVIEW

8.17: Fungi

Topic hierarchy

8.17A: Characteristics of Fungi

8.17B: Fungi as Plant, Animal, and Human Pathogens

8.17C: Fungi Habitat, Decomposition, and Recycling

8.17D: Chytridiomycota - The Chytrids

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8.17G: Ascomycota - The Sac Fungi

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8.17A: Characteristics of Fungi

Characteristics of Fungi

Fungi, latin for mushroom, are eukaryotes which are responsible for decomposition and nutrient cycling through the environment.

LEARNING OBJECTIVES

Describe the role of fungi in the ecosystem

KEY TAKEAWAYS

Key Points

- Fungi are more closely related to animals than plants.
- Fungi are heterotrophic: they use complex organic compounds as sources of energy and carbon, not photosynthesis.
- Fungi multiply either asexually, sexually, or both.
- The majority of fungi produce spores, which are defined as haploid cells that can undergo mitosis to form multicellular, haploid individuals.
- Fungi interact with other organisms by either forming beneficial or mutualistic associations (mycorrhizae and lichens) or by causing serious infections.

Key Terms

- **mycorrhiza**: a symbiotic association between a fungus and the roots of a vascular plant
- **spore**: a reproductive particle, usually a single cell, released by a fungus, alga, or plant that may germinate into another
- **lichen**: any of many symbiotic organisms, being associations of fungi and algae; often found as white or yellow patches on old walls, etc.
- **Ascomycota**: a taxonomic division within the kingdom Fungi; those fungi that produce spores in a microscopic sporangium called an ascus
- **heterotrophic**: organisms that use complex organic compounds as sources of energy and carbon

Introduction to Fungi

The word fungus comes from the Latin word for mushrooms. Indeed, the familiar mushroom is a reproductive structure used by many types of fungi. However, there are also many fungi species that don't produce mushrooms at all. Being eukaryotes, a typical fungal cell contains a true nucleus and many membrane-bound organelles. The kingdom Fungi includes an enormous variety of living organisms collectively referred to as Ascomycota, or true Fungi. While scientists have identified about 100,000 species of fungi, this is only a fraction of the 1.5 million species of fungus probably present on earth. Edible mushrooms, yeasts, black mold, and the producer of the antibiotic penicillin, *Penicilliumnotatum*, are all members of the kingdom Fungi, which belongs to the domain Eukarya.



Figure: **Examples of fungi**: Many species of fungus produce the familiar mushroom (a) which is a reproductive structure. This (b) coral fungus displays brightly-colored fruiting bodies. This electron micrograph shows (c) the spore-bearing structures of Aspergillus, a type of toxic fungi found mostly in soil and plants.

Fungi, once considered plant-like organisms, are more closely related to animals than plants. Fungi are not capable of photosynthesis: they are heterotrophic because they use complex organic compounds as sources of energy and carbon. Some fungal organisms multiply only asexually, whereas others undergo both asexual reproduction and sexual reproduction with alternation of generations. Most fungi produce a large number of spores, which are haploid cells that can undergo mitosis to form multicellular,

haploid individuals. Like bacteria, fungi play an essential role in ecosystems because they are decomposers and participate in the cycling of nutrients by breaking down organic and inorganic materials to simple molecules.

Fungi often interact with other organisms, forming beneficial or mutualistic associations. For example most terrestrial plants form symbiotic relationships with fungi. The roots of the plant connect with the underground parts of the fungus forming mycorrhizae. Through mycorrhizae, the fungus and plant exchange nutrients and water, greatly aiding the survival of both species Alternatively, lichens are an association between a fungus and its photosynthetic partner (usually an alga). Fungi also cause serious infections in plants and animals. For example, Dutch elm disease, which is caused by the fungus *Ophiostoma ulmi*, is a particularly devastating type of fungal infestation that destroys many native species of elm (*Ulmus* sp.) by infecting the tree's vascular system. The elm bark beetle acts as a vector, transmitting the disease from tree to tree. Accidentally introduced in the 1900s, the fungus decimated elm trees across the continent. Many European and Asiatic elms are less susceptible to Dutch elm disease than American elms.

In humans, fungal infections are generally considered challenging to treat. Unlike bacteria, fungi do not respond to traditional antibiotic therapy because they are eukaryotes. Fungal infections may prove deadly for individuals with compromised immune systems.

Fungi have many commercial applications. The food industry uses yeasts in baking, brewing, and cheese and wine making. Many industrial compounds are byproducts of fungal fermentation. Fungi are the source of many commercial enzymes and antibiotics.

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8.17B: Fungi as Plant, Animal, and Human Pathogens

From crop and food spoilage to severe infections in animal species, fungal parasites and pathogens are wide spread and difficult to treat.

Learning Objectives

- Give examples of fungi that are plant and animal parasites and pathogens

Key Points

- In plants, fungi can destroy plant tissue directly or through the production of potent toxins, which usually ends in host death and can even lead to ergotism in animals like humans.
- During mycosis, fungi, like dermatophytes, successfully attack hosts directly by colonizing and destroying their tissues.
- Examples of fungal parasites and pathogens in animals that cause mycoses include *Batrachochytrium dendrobatidis*, *Geomyces destructans*, and *Histoplasma capsulatum*.
- Systemic mycoses, such as valley fever, Histoplasmosis, or pulmonary disease, are fungal diseases that spread to internal organs and commonly enter the body through the respiratory system.
- Opportunistic mycoses, fungal infections that are common in all environments, mainly take advantage of individuals who have a compromised immune system, such as AIDS patients.
- Fungi can also cause mycetismus, a disease caused by the ingestion of toxic mushrooms that leads to poisoning.

Key Terms

- **mycosis**: a fungal disease caused by infection and direct damage
- **dermatophyte**: a parasitic fungus that secretes extracellular enzymes that break down keratin, causing infections the skin, such as jock itch and athlete's foot
- **aflatoxin**: toxic, carcinogenic compounds released by fungi of the genus Aspergillus; contaminate nut and grain harvests
- **ergot**: any fungus in the genus Claviceps which are parasitic on grasses

Fungal Parasites and Pathogens

The production of sufficient good-quality crops is essential to human existence. Plant diseases have ruined crops, bringing widespread famine. Many plant pathogens are fungi that cause tissue decay and eventual death of the host. In addition to destroying plant tissue directly, some plant pathogens spoil crops by producing potent toxins. Fungi are also responsible for food spoilage and the rotting of stored crops. For example, the fungus *Claviceps purpurea* causes ergot, a disease of cereal crops (especially of rye). Although the fungus reduces the yield of cereals, the effects of the ergot's alkaloid toxins on humans and animals are of much greater significance. In animals, the disease is referred to as ergotism. The most common signs and symptoms are convulsions, hallucinations, gangrene, and loss of milk in cattle. The active ingredient of ergot is lysergic acid, which is a precursor of the drug LSD. Smuts, rusts, and powdery or downy mildew are other examples of common fungal pathogens that affect crops.



Figure: **Fungal pathogens**: Some fungal pathogens include (a) green mold on grapefruit, (b) powdery mildew on a zinnia, (c) stem rust on a sheaf of barley, and (d) grey rot on grapes.

Aflatoxins are toxic, carcinogenic compounds released by fungi of the genus *Aspergillus*. Periodically, harvests of nuts and grains are tainted by aflatoxins, leading to massive recall of produce. This sometimes ruins producers and causes food shortages in developing countries.

Animal and Human Parasites and Pathogens

Fungi can affect animals, including humans, in several ways. A mycosis is a fungal disease that results from infection and direct damage. Fungi attack animals directly by colonizing and destroying tissues. Mycotoxicosis is the poisoning of humans (and other animals) by foods contaminated by fungal toxins (mycotoxins). Mycetismus describes the ingestion of preformed toxins in poisonous mushrooms. In addition, individuals who display hypersensitivity to molds and spores develop strong and dangerous allergic reactions. Fungal infections are generally very difficult to treat because, unlike bacteria, fungi are eukaryotes. Antibiotics only target prokaryotic cells, whereas compounds that kill fungi also harm the eukaryotic animal host.

Many fungal infections are superficial; that is, they occur on the animal's skin. Termed cutaneous ("skin") mycoses, they can have devastating effects. For example, the decline of the world's frog population in recent years may be caused by the fungus *Batrachochytrium dendrobatidis*, which infects the skin of frogs and presumably interferes with gaseous exchange. Similarly, more than a million bats in the United States have been killed by white-nose syndrome, which appears as a white ring around the mouth of the bat. It is caused by the cold-loving fungus *Geomyces destructans*, which disseminates its deadly spores in caves where bats hibernate. Mycologists are researching the transmission, mechanism, and control of *G. destructans* to stop its spread.

Fungi that cause the superficial mycoses of the epidermis, hair, and nails rarely spread to the underlying tissue. These fungi are often misnamed "dermatophytes", from the Greek words dermis meaning skin and phyte meaning plant, although they are not plants. Dermatophytes are also called "ringworms" because of the red ring they cause on skin. They secrete extracellular enzymes that break down keratin (a protein found in hair, skin, and nails), causing conditions such as athlete's foot and jock itch. These conditions are usually treated with over-the-counter topical creams and powders; they are easily cleared. More persistent superficial mycoses may require prescription oral medications.

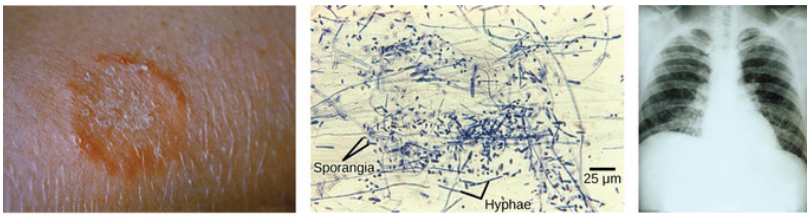

Figure: **Mycosis infection**: (a) Ringworm presents as a red ring on skin; (b) *Trichophyton violaceum*, shown in this bright field light micrograph, causes superficial mycoses on the scalp; (c) *Histoplasma capsulatum* is an ascomycete that infects airways and causes symptoms similar to influenza.

Systemic mycoses spread to internal organs, most commonly entering the body through the respiratory system. For example, coccidioidomycosis (valley fever) is commonly found in the southwestern United States where the fungus resides in the dust. Once inhaled, the spores develop in the lungs and cause symptoms similar to those of tuberculosis. Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. It also causes pulmonary infections. In rarer cases, it causes swelling of the membranes of the brain and spinal cord. Treatment of these and many other fungal diseases requires the use of antifungal medications that have serious side effects.

Opportunistic mycoses are fungal infections that are either common in all environments or are part of the normal biota. They mainly affect individuals who have a compromised immune system. Patients in the late stages of AIDS suffer from opportunistic mycoses that can be life threatening. The yeast *Candida sp.*, a common member of the natural biota, can grow unchecked and infect the vagina or mouth (oral thrush) if the pH of the surrounding environment, the person's immune defenses, or the normal population of bacteria are altered.

Mycetismus can occur when poisonous mushrooms are eaten. It causes a number of human fatalities during mushroom-picking season. Many edible fruiting bodies of fungi resemble highly-poisonous relatives. Amateur mushroom hunters are cautioned to carefully inspect their harvest and avoid eating mushrooms of doubtful origin.

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8.17C: Fungi Habitat, Decomposition, and Recycling

Fungi are the major decomposers of nature; they break down organic matter which would otherwise not be recycled.

Learning Objectives

- Explain the roles played by fungi in decomposition and recycling

Key Points

- Aiding the survival of species from other kingdoms through the supply of nutrients, fungi play a major role as decomposers and recyclers in the wide variety of habitats in which they exist.
- Fungi provide a vital role in releasing scarce, yet biologically-essential elements, such as nitrogen and phosphorus, from decaying matter.
- Their mode of nutrition, which involves digestion before ingestion, allows fungi to degrade many large and insoluble molecules that would otherwise remain trapped in a habitat.

Key Terms

- **decomposer**: any organism that feeds off decomposing organic material, especially bacterium or fungi
- **exoenzyme**: any enzyme, generated by a cell, that functions outside of that cell
- **saprobe**: an organism that lives off of dead or decaying organic material

Fungi & Their Roles as Decomposers and Recyclers

Fungi play a crucial role in the balance of ecosystems. They colonize most habitats on earth, preferring dark, moist conditions. They can thrive in seemingly-hostile environments, such as the tundra. However, most members of the Kingdom Fungi grow on the forest floor where the dark and damp environment is rich in decaying debris from plants and animals. In these environments, fungi play a major role as decomposers and recyclers, making it possible for members of the other kingdoms to be supplied with nutrients and to live.

The food web would be incomplete without organisms that decompose organic matter. Some elements, such as nitrogen and phosphorus, are required in large quantities by biological systems; yet, they are not abundant in the environment. The action of fungi releases these elements from decaying matter, making them available to other living organisms. Trace elements present in low amounts in many habitats are essential for growth, but would remain tied up in rotting organic matter if fungi and bacteria did not return them to the environment via their metabolic activity.



Figure: **Fungi as decomposers**: Fungi are an important part of ecosystem nutrient cycles. These bracket fungi growing on the side of a tree are the fruiting structures of a basidiomycete. They receive their nutrients through their hyphae, which invade and decay the tree trunk.

The ability of fungi to degrade many large and insoluble molecules is due to their mode of nutrition. As seen earlier, digestion precedes ingestion. Fungi produce a variety of exoenzymes to digest nutrients. These enzymes are either released into the substrate or remain bound to the outside of the fungal cell wall. Large molecules are broken down into small molecules, which are transported into the cell by a system of protein carriers embedded in the cell membrane. Because the movement of small molecules and enzymes is dependent on the presence of water, active growth depends on a relatively-high percentage of moisture in the environment.

As saprobes, fungi help maintain a sustainable ecosystem for the animals and plants that share the same habitat. In addition to replenishing the environment with nutrients, fungi interact directly with other organisms in beneficial, but sometimes damaging, ways.



Figure: **Fungi: beneficial & pathogenic**: Shelf fungi, so called because they grow on trees in a stack, attack and digest the trunk or branches of a tree. While some shelf fungi are found only on dead trees, others can parasitize living trees, causing eventual death. They are considered serious tree pathogens.

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8.17D: Chytridiomycota - The Chytrids

Chytrids are the most primitive group of fungi and the only group that possess gametes with flagella.

Learning Objectives

- Describe the ecology and reproduction of chytrids

Key Points

- The first recognizable chytrids appeared more than 500 million years ago during the late pre-Cambrian period.
- Like protists, chytrids usually live in aquatic environments, but some species live on land.
- Some chytrids are saprobes while others are parasites that may be harmful to amphibians and other animals.
- Chytrids reproduce both sexually and asexually, which leads to the production of zoospores.
- Chytrids have chitin in their cell walls; one unique group also has cellulose along with chitin.
- Chytrids are mostly unicellular, but multicellular organisms do exist.

Key Terms

- **chytridiomycete**: an organism of the phylum Chytridiomycota
- **zoospore**: an asexual spore of some algae and fungi
- **flagellum**: a flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells
- **coenocytic**: a multinucleate cell that can result from multiple nuclear divisions without their accompanying cytokinesis

Chytridiomycota: The Chytrids

The kingdom Fungi contains five major phyla, which were established according to their mode of sexual reproduction or use of molecular data. The Phylum Chytridiomycota (chytrids) is one of the five true phyla of fungi. There is only one class in the Phylum Chytridiomycota, the Chytridiomycetes. The chytrids are the simplest and most primitive Eumycota, or true fungi. The evolutionary record shows that the first, recognizable chytrids appeared during the late pre-Cambrian period, more than 500 million years ago. Like all fungi, chytrids have chitin in their cell walls, but one group of chytrids has both cellulose and chitin in the cell wall. Most chytrids are unicellular; a few form multicellular organisms and hyphae, which have no septa between cells (coenocytic). They reproduce both sexually and asexually; the asexual spores are called diploid zoospores. Their gametes are the only fungal cells known to have a flagellum.

The ecological habitat and cell structure of chytrids have much in common with protists. Chytrids usually live in aquatic environments, although some species live on land. Some species thrive as parasites on plants, insects, or amphibians, while others are saprobes. Some chytrids cause diseases in many species of amphibians, resulting in species decline and extinction. An example of a harmful parasitic chytrid is *Batrachochytrium dendrobatidis*, which is known to cause skin disease. Another chytrid species, *Allomyces*, is well characterized as an experimental organism. Its reproductive cycle includes both asexual and sexual phases. *Allomyces* produces diploid or haploid flagellated zoospores in a sporangium.

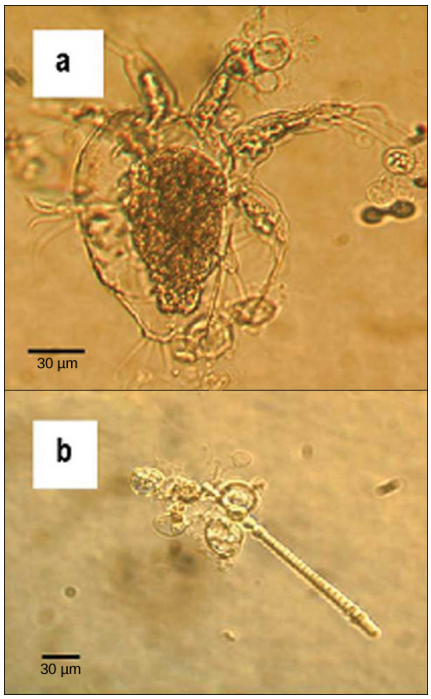

Figure: **Parasitic chytrids**: The chytrid *Batrachochytrium dendrobatidis* is seen in these light micrographs as transparent spheres growing on (a) a freshwater arthropod and (b) algae. This chytrid causes skin diseases in many species of amphibians, resulting in species decline and extinction.

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8.17E: Zygomycota - The Conjugated Fungi

Zygomycota, a small group in the fungi kingdom, can reproduce asexually or sexually, in a process called conjugation.

Learning Objectives

- Describe the ecology and reproduction of Zygomycetes

Key Points

- Most zygomycota are saprobes, while a few species are parasites.
- Zygomycota usually reproduce asexually by producing sporangiospores.
- Zygomycota reproduce sexually when environmental conditions become unfavorable.
- To reproduce sexually, two opposing mating strains must fuse or conjugate, thereby, sharing genetic content and creating zygospores.
- The resulting diploid zygospores remain dormant and protected by thick coats until environmental conditions have improved.
- When conditions become favorable, zygospores undergo meiosis to produce haploid spores, which will eventually grow into a new organism.

Key Terms

- **zygomycete**: an organism of the phylum Zygomycota
- **karyogamy**: the fusion of two nuclei within a cell
- **zygospore**: a spore formed by the union of several zoospores
- **conjugation**: the temporary fusion of organisms, especially as part of sexual reproduction

Zygomycota: The Conjugated Fungi

The zygomycetes are a relatively small group in the fungi kingdom and belong to the Phylum Zygomycota. They include the familiar bread mold, *Rhizopus stolonifer*, which rapidly propagates on the surfaces of breads, fruits, and vegetables. They are mostly terrestrial in habitat, living in soil or on plants and animals. Most species are saprobes meaning they live off decaying organic material. Some are parasites of plants, insects, and small animals, while others form symbiotic relationships with plants. Zygomycetes play a considerable commercial role. The metabolic products of other species of *Rhizopus* are intermediates in the synthesis of semi-synthetic steroid hormones.

Zygomycetes have a thallus of coenocytic hyphae in which the nuclei are haploid when the organism is in the vegetative stage. The fungi usually reproduce asexually by producing sporangiospores. The black tips of bread mold, *Rhizopus stolonifer*, are the swollen sporangia packed with black spores. When spores land on a suitable substrate, they germinate and produce a new mycelium.

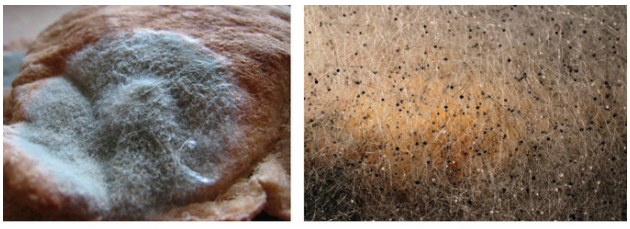

Figure: **Sporangia of bread mold**: Sporangia grow at the end of stalks, which appear as (a) white fuzz seen on this bread mold, *Rhizopus stolonifer*. The (b) tips of bread mold are the spore-containing sporangia.

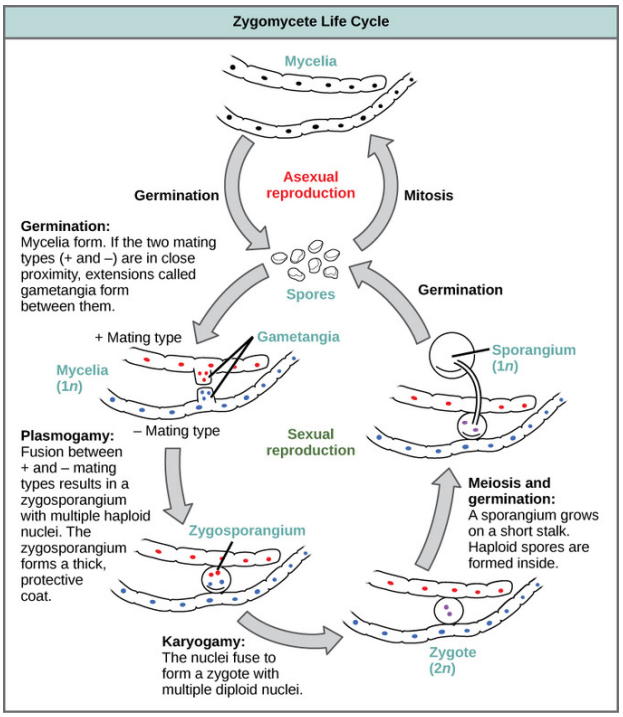

Figure: **Zygomycete life cycle**: Zygomycetes have asexual and sexual life cycles. In the sexual life cycle, plus and minus mating types conjugate to form a zygosporangium.

Sexual reproduction starts when conditions become unfavorable. Two opposing mating strains (type + and type –) must be in close proximity for gametangia (singular: gametangium) from the hyphae to be produced and fuse, leading to karyogamy. The developing diploid zygospores have thick coats that protect them from desiccation and other hazards. They may remain dormant until environmental conditions become favorable. When the zygospore germinates, it undergoes meiosis and produces haploid spores, which will, in turn, grow into a new organism. This form of sexual reproduction in fungi is called conjugation (although it differs markedly from conjugation in bacteria and protists), giving rise to the name “conjugated fungi”.

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8.17F: Glomeromycota

Learning Objectives

- Describe the ecology and reproduction of Glomeromycetes

In the kingdom Fungi, the Glomeromycota is a newly-established phylum comprised of about 230 species that live in close association with the roots of trees and plants. Fossil records indicate that trees and their root symbionts share a long evolutionary history. It appears that most members of this family form arbuscular mycorrhizae: the hyphae interact with the root cells forming a mutually-beneficial association where the plants supply the carbon source and energy in the form of carbohydrates to the fungus while the fungus supplies essential minerals from the soil to the plant. This association is termed biotrophic. The Glomeromycota species that have arbuscular mycorrhizal are terrestrial and widely distributed in soils worldwide where they form symbioses with the roots of the majority of plant species. They can also be found in wetlands, including salt-marshes, and are associated with epiphytic plants.

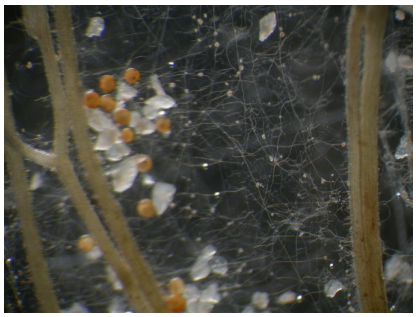

Figure: ***Glyomeromycetes and tree roots****: This image illustrates the bitrophic relationship between a glomeromycota (Gigaspora margarita) and the roots of a plant (Lotus corniculatus).*

The glomeromycetes do not reproduce sexually and cannot survive without the presence of plant roots. They have coenocytic hyphae and reproduce asexually, producing glomerospores. The biochemical and genetic characterization of the Glomeromycota has been hindered by their biotrophic nature, which impedes laboratory culturing. This obstacle was eventually surpassed with the use of root cultures. With the advent of molecular techniques, such as gene sequencing, the phylogenetic classification of Glomeromycota has become clearer. The first mycorrhizal gene to be sequenced was the small-subunit ribosomal RNA (SSU rRNA). This gene is highly conserved and commonly used in phylogenetic studies so it was isolated from spores of each taxonomic group. Using a molecular clock approach based on the substitution rates of SSU sequences, scientists were able to estimate the time of divergence of the fungi. This analysis shows that all glomeromycetes probably descended from a common ancestor 462 and 353 million years ago, making them a monophyletic lineage. A long-held theory is that Glomeromycota were instrumental in the colonization of land by plants.

Key Points

- Most glomeromycetes form arbuscular mycorrhizae, a type of symbiotic relationship between a fungus and plant roots; the plants supply a source of energy to the fungus while the fungus supplies essential minerals to the plant.
- Glomeromycota that have arbuscular mycorrhizal are mostly terrestrial, but can also be found in wetlands.
- The glomeromycetes reproduce asexually by producing glomerospores and cannot survive without the presence of plant roots.
- DNA analysis shows that all glomeromycetes probably descended from a common ancestor 462 and 353 million years ago.
- The classification of fungi as Glomeromycota has been redefined with adoption of molecular techniques.

Key Terms

- **biotrophic**: describing a parasite that needs its host to stay alive
- **arbuscular mycorrhizae**: a type of symbiotic relationship between a fungus and the roots of a plant where the plants supply a source of energy to the fungus while the fungus supplies essential minerals to the plant
- **glomeromycete**: an organism of the phylum Glomeromycota

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8.17G: Ascomycota - The Sac Fungi

Most fungi belong to the Phylum Ascomycota, which uniquely forms of an ascus, a sac-like structure that contains haploid ascospores.

Learning Objectives

- Describe the ecology and the reproduction of Ascomycetes

Key Points

- Ascomycota fungi are the yeasts used in baking, brewing, and wine fermentation, plus delicacies such as truffles and morels.
- Ascomycetes are filamentous and produce hyphae divided by perforated septa.
- Ascomycetes frequently reproduce asexually which leads to the production of conidiophores that release haploid conidiospores.
- Two types of mating strains, a “male” strain which produces an antheridium and a “female” strain which develops an ascogonium, are required for sexual reproduction.
- The antheridium and the ascogonium combine in plasmogamy at the time of fertilization, followed by nuclei fusion in the asci.
- In the ascocarp, a fruiting body, thousands of asci undergo meiosis to generate haploid ascospores ready to be released to the world.

Key Terms

- **plasmogamy**: stage of sexual reproduction joining the cytoplasm of two parent mycelia without the fusion of nuclei
- **Ascomycota**: a taxonomic division within the kingdom Fungi; those fungi that produce spores in a microscopic sporangium called an ascus
- **ascus**: a sac-shaped cell present in ascomycete fungi; it is a reproductive cell in which meiosis and an additional cell division produce eight spores
- **ascospore**: a sexually-produced spore from the ascus of an Ascomycetes fungus
- **conidia**: asexual, non-motile spores of a fungus, named after the Greek word for dust, conia; also known as conidiospores and mitospores
- **antheridia**: a haploid structure or organ producing and containing male gametes (called antherozoids or sperm) present in lower plants like mosses and ferns, primitive vascular psilotophytes, and fungi
- **ascogonium**: a haploid structure or organ producing and containing female gametes in certain Ascomycota fungi
- **ascocarp**: the sporocarp of an ascomycete, typically bowl-shaped
- **ascomycete**: any fungus of the phylum Ascomycota, characterized by the production of a sac, or ascus, which contains non-motile spores

Ascomycota: The Sac Fungi

The majority of known fungi belong to the Phylum Ascomycota, which is characterized by the formation of an ascus (plural, asci), a sac-like structure that contains haploid ascospores. Many ascomycetes are of commercial importance. Some play a beneficial role, such as the yeasts used in baking, brewing, and wine fermentation, plus truffles and morels, which are held as gourmet delicacies. *Aspergillus oryzae* is used in the fermentation of rice to produce sake. Other ascomycetes parasitize plants and animals, including humans. For example, fungal pneumonia poses a significant threat to AIDS patients who have a compromised immune system. Ascomycetes not only infest and destroy crops directly, they also produce poisonous secondary metabolites that make crops unfit for consumption. Filamentous ascomycetes produce hyphae divided by perforated septa, allowing streaming of cytoplasm from one cell to the other. Conidia and asci, which are used respectively for asexual and sexual reproductions, are usually separated from the vegetative hyphae by blocked (non-perforated) septa.

Asexual reproduction is frequent and involves the production of conidiophores that release haploid conidiospores. Sexual reproduction starts with the development of special hyphae from either one of two types of mating strains. The “male” strain produces an antheridium (plural: antheridia) and the “female” strain develops an ascogonium (plural: ascogonia). At fertilization, the antheridium and the ascogonium combine in plasmogamy without nuclear fusion. Special ascogenous hyphae arise, in which pairs of nuclei migrate: one from the “male” strain and one from the “female” strain. In each ascus, two or more haploid ascospores fuse their nuclei in karyogamy. During sexual reproduction, thousands of asci fill a fruiting body called the ascocarp. The diploid

nucleus gives rise to haploid nuclei by meiosis. The ascospores are then released, germinate, and form hyphae that are disseminated in the environment and start new mycelia.

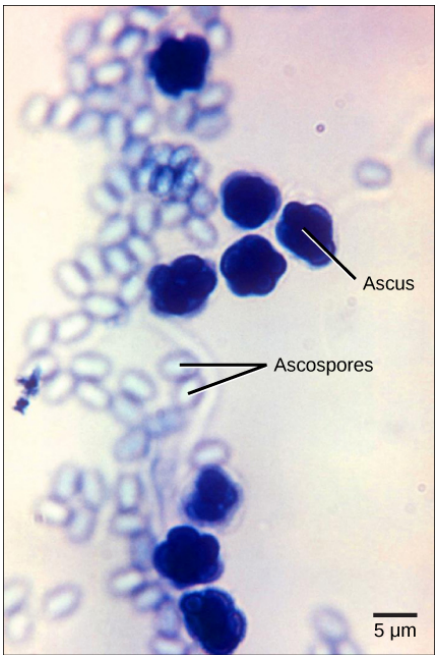

Figure: **Release of ascospores**: The bright field light micrograph shows ascospores being released from asci in the fungus Talaromyces flavus var. flavus.

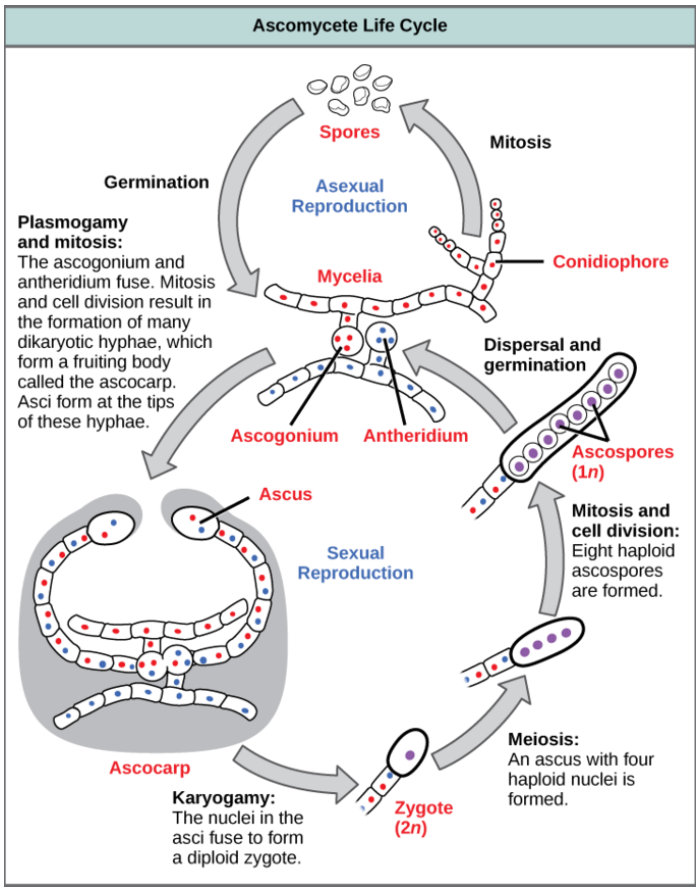

Figure: **Lifecycle of an ascomycete**: The lifecycle of an ascomycete is characterized by the production of asci during the sexual phase. The haploid phase is the predominant phase of the life cycle.

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8.17H: Basidiomycota - The Club Fungi

The basidiomycota are mushroom-producing fungi with developing, club-shaped fruiting bodies called basidia on the gills under its cap.

Learning Objectives

- Describe the ecology and reproduction of the Basidiomycota

Key Points

- The majority of edible fungi belong to the Phylum Basidiomycota.
- The basidiomycota includes shelf fungus, toadstools, and smuts and rusts.
- Unlike most fungi, basidiomycota reproduce sexually as opposed to asexually.
- Two different mating strains are required for the fusion of genetic material in the basidium which is followed by meiosis producing haploid basidiospores.
- Mycelia of different mating strains combine to produce a secondary mycelium that contains haploid basidiospores in what is called the dikaryotic stage, where the fungi remains until a basidiocarp (mushroom) is generated with the developing basidia on the gills under its cap.

Key Terms

- **basidiocarp**: a fruiting body that protrudes from the ground, known as a mushroom, which has a developing basidia on the gills under its cap
- **basidiomycete**: a fungus of the phylum Basidiomycota, which produces sexual spores on a basidium
- **Basidiomycota**: a taxonomic division within the kingdom Fungi: 30,000 species of fungi that produce spores from a basidium
- **basidium**: a small structure, shaped like a club, found in the Basidiomycota phylum of fungi, that bears four spores at the tips of small projections
- **basidiospore**: a sexually-reproductive spore produced by fungi of the phylum Basidiomycota

Basidiomycota: The Club Fungi



Figure: **Fruiting bodies of a basidiomycete**: The fruiting bodies of a basidiomycete form a ring in a meadow, commonly called "fairy ring." The best-known fairy ring fungus has the scientific name *Marasmius oreades*. The body of this fungus, its mycelium, is underground and grows outward in a circle. As it grows, the mycelium depletes the soil of nitrogen, causing the mycelia to grow away from the center, leading to the "fairy ring" of fruiting bodies where there is adequate soil nitrogen.

The fungi in the Phylum Basidiomycota are easily recognizable under a light microscope by their club-shaped fruiting bodies called basidia (singular, basidium), which are the swollen terminal cell of a hypha. The basidia, which are the reproductive organs of these fungi, are often contained within the familiar mushroom, commonly seen in fields after rain, on the supermarket shelves, and growing on your lawn. These mushroom-producing basidiomyces are sometimes referred to as "gill fungi" because of the presence of gill-like structures on the underside of the cap. The "gills" are actually compacted hyphae on which the basidia are borne. This group also includes shelf fungus, which cling to the bark of trees like small shelves. In addition, the basidiomycota includes smuts and rusts, which are important plant pathogens, and toadstools. Most edible fungi belong to the Phylum Basidiomycota; however, some basidiomycetes produce deadly toxins. For example, *Cryptococcus neoformans* causes severe respiratory illness.

The lifecycle of basidiomycetes includes alternation of generations. Spores are generally produced through sexual reproduction, rather than asexual reproduction. The club-shaped basidium carries spores called basidiospores. In the basidium, nuclei of two different mating strains fuse (karyogamy), giving rise to a diploid zygote that then undergoes meiosis. The haploid nuclei migrate into basidiospores, which germinate and generate monokaryotic hyphae. The mycelium that results is called a primary mycelium. Mycelia of different mating strains can combine and produce a secondary mycelium that contains haploid nuclei of two different mating strains. This is the dikaryotic stage of the basidiomyces lifecyle and it is the dominant stage. Eventually, the secondary mycelium generates a basidiocarp, which is a fruiting body that protrudes from the ground; this is what we think of as a mushroom. The basidiocarp bears the developing basidia on the gills under its cap.

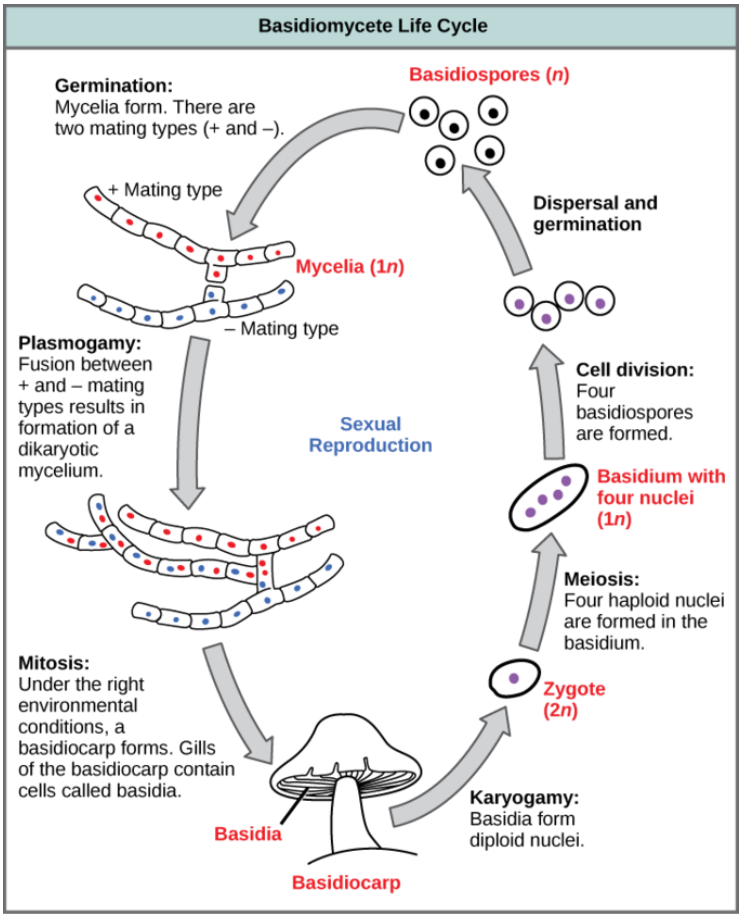

Figure: **Lifecycle of a basidiomycete**: The lifecycle of a basidiomycete alternates generation with a prolonged stage in which two nuclei (dikaryon) are present in the hyphae.

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SECTION OVERVIEW

8.18: Protists

Topic hierarchy

8.18A: Early Eukaryotes

8.18B: Excavata

8.18C: Chromalveolata: Alveolates

8.18D: Chromalveolata: Stramenopiles

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8.18F: Amoebozoa and Opisthokonta

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8.18A: Early Eukaryotes

Protists are eukaryotes that first appeared approximately 2 billion years ago with the rise of atmospheric oxygen levels.

Learning Objectives

- Discuss the origins of eukaryotes in terms of the geologic time line

Key Points

- On a geological time line, protists are among the first organisms that evolved after prokaryotes.
- Today's eukaryotes evolved from a common ancestor with the following features: a nucleus that divided via mitosis, DNA associated with histones, a cytoskeleton and endomembrane system, the ability to make cilia/flagella.
- Protists vary widely in size, from single cells approximately 10 µm in size to multicellular seaweeds that are visible with the naked eye.

Key Terms

- **cyanobacteria**: photosynthetic prokaryotic microorganisms, of phylum Cyanobacteria, once known as blue-green algae
- **aerobic**: living or occurring only in the presence of oxygen
- **endomembrane**: all the membraneous components inside a eukaryotic cell, including the nuclear envelope, endoplastic reticulum, and Golgi apparatus

Origins of Eukaryotes

Humans have been familiar with macroscopic organisms (organisms big enough to see with the unaided eye) since before there was a written history. It is likely that most cultures distinguished between animals and land plants, but most probably included the macroscopic fungi as plants. Therefore, it became an interesting challenge to deal with the world of microorganisms once microscopes were developed a few centuries ago. Many different naming schemes were used over the last couple of centuries, but it has become the most common practice to refer to eukaryotes that are not land plants, animals, or fungi as protists.

Most protists are microscopic, unicellular organisms that are abundant in soil, freshwater, brackish, and marine environments. They are also common in the digestive tracts of animals and in the vascular tissues of plants. Others invade the cells of other protists, animals, and plants. Not all protists are microscopic. Some have huge, macroscopic cells, such as the plasmodia (giant amoebae) of myxomycete slime molds or the marine green alga *Caulerpa*, which can have single cells that can be several meters in size. Some protists are multicellular, such as the red, green, and brown seaweeds. It is among the protists that one finds the wealth of ways that organisms can grow. They are among the first organisms to evolve with the rise of eukaryotes.

Eukaryotes in a Geological Time Frame

The oldest fossil evidence of eukaryotes, cells measuring 10 µm or greater, is about 2 billion years old. All fossils older than this appear to be prokaryotes. It is probable that today's eukaryotes are descended from an ancestor that had a prokaryotic cellular organization. The last common ancestor (LCA) of today's Eukarya had several characteristics that included: cells with nuclei that divided mitotically and contained linear chromosomes where the DNA was associated with histones; a cytoskeleton and endomembrane system; and the ability to make cilia/flagella during at least part of its life cycle. The LCA was aerobic because it had mitochondria that were the result of an aerobic alpha-proteobacterium that lived inside a host cell. Whether this host had a nucleus at the time of the initial symbiosis remains unknown. The LCA may have had a cell wall for at least part of its life cycle, but more data are needed to confirm this hypothesis. Today's eukaryotes are very diverse in their shapes, organization, life cycles, and number of cells per individual.

While today's atmosphere is about one-fifth molecular oxygen (O_2), geological evidence shows that it originally lacked O_2. Without oxygen, aerobic respiration would not be expected; living things would have relied on fermentation instead. At some point before about 3.5 billion years ago, some prokaryotes evolved the ability to photosynthesize. Cyanobacteria used water as a hydrogen source and released O_2 as a waste product. Originally, oxygen-rich environments were probably localized around places where cyanobacteria were active, but by about 2 billion years ago, geological evidence shows that oxygen was building up to higher concentrations in the atmosphere. Oxygen levels similar to today's levels only arose within the last 700 million years. Recall that the first fossils that we believe to be eukaryotes date to about 2 billion years old, so they appeared as oxygen levels were increasing.

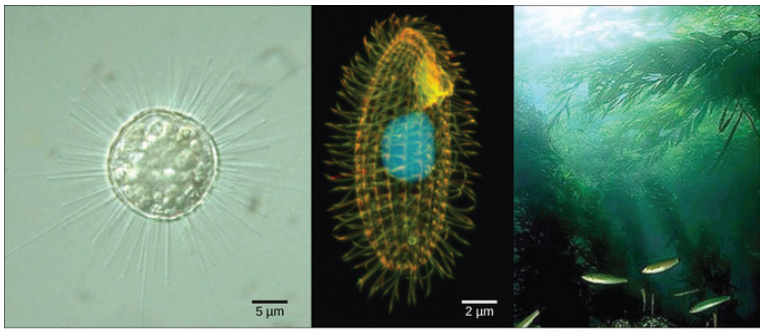

Figure: **Protist varieties**: Protists range from the microscopic, single-celled (a) Acanthocystis turfacea and the (b) ciliate Tetrahymena thermophila, both visualized here using light microscopy, to the enormous, multicellular (c) kelps (Chromalveolata) that extend for hundreds of feet in underwater "forests. "

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8.18B: Excavata

Excavata, defined by a feeding groove that is “excavated” from one side, includes Diplomonads, Parabasalids and Euglenozoans.

Learning Objectives

- Describe characteristics of Excavates, including Diplomonads, Parabasalids and Euglenozoans

Key Points

- Excavata are a supergroup of protists that are defined by an asymmetrical appearance with a feeding groove that is “excavated” from one side; it includes various types of organisms which are parasitic, photosynthetic and heterotrophic predators.
- Excavata includes the protists: Diplomonads, Parabasalids and Euglenozoans.
- Diplomonads are defined by the presence of a nonfunctional, mitochrondrial-remnant organelle called a mitosome.
- Parabasalids are characterized by a semi-functional mitochondria referred to as a hydrogenosome; they are comprised of parasitic protists, such as *Trichomonas vaginalis*.
- Euglenozoans can be classified as mixotrophs, heterotrophs, autotrophs, and parasites; they are defined by their use of flagella for movement.

Key Terms

- **mitosome**: an organelle found within certain unicellular eukaryotes which lack mitochondria
- **hydrogenosome**: a membrane-bound organelle found in ciliates, trichomonads, and fungi which produces molecular hydrogen and ATP
- **kinetoplast**: a disk-shaped mass of circular DNA inside a large mitochondrion, found specifically in protozoa of the class Kinetoplastea

Excavata

Many of the protist species classified into the supergroup Excavata are asymmetrical, single-celled organisms with a feeding groove “excavated” from one side. This supergroup includes heterotrophic predators, photosynthetic species, and parasites. Its subgroups are the diplomonads, parabasalids, and euglenozoans.

Diplomonads

Among the Excavata are the diplomonads, which include the intestinal parasite, *Giardia lamblia*. Until recently, these protists were believed to lack mitochondria. Mitochondrial remnant organelles, called mitosomes, have since been identified in diplomonads, but these mitosomes are essentially nonfunctional. Diplomonads exist in anaerobic environments and use alternative pathways, such as glycolysis, to generate energy. Each diplomonad cell has two identical nuclei and uses several flagella for locomotion.



Figure: ***Giardia lamblia.*** The intestinal parasite *Giardia lamblia*, visualized here using scanning electron microscopy, is a waterborne protist that causes severe diarrhea when ingested.

Parabasalids

A second Excavata subgroup, the parabasalids, also exhibits semi-functional mitochondria. In parabasalids, these structures function anaerobically and are called hydrogenosomes because they produce hydrogen gas as a byproduct. Parabasalids move with flagella and membrane rippling. *Trichomonas vaginalis*, a parabasalid that causes a sexually-transmitted disease in humans, employs these mechanisms to transit through the male and female urogenital tracts. *T. vaginalis* causes trichomoniasis, which appears in an estimated 180 million cases worldwide each year. Whereas men rarely exhibit symptoms during an infection with this protist, infected women may become more susceptible to secondary infection with human immunodeficiency virus (HIV) or genital wart virus infection, which causes over 90% of cervical cancer. Pregnant women infected with *T. vaginalis* are at an increased risk of serious complications, such as pre-term delivery.

Euglenozoans

Euglenozoans includes parasites, heterotrophs, autotrophs, and mixotrophs, ranging in size from 10 to 500 µm. Euglenoids move through their aquatic habitats using two long flagella that guide them toward light sources sensed by a primitive ocular organ called an eyespot. The familiar genus, *Euglena*, encompasses some mixotrophic species that display a photosynthetic capability only when light is present. In the dark, the chloroplasts of *Euglena* shrink up and temporarily cease functioning; the cells, instead, take up organic nutrients from their environment.

The human parasite, *Trypanosoma brucei*, belongs to a different subgroup of Euglenozoa, the kinetoplastids. The kinetoplastid subgroup is named after the kinetoplast, a DNA mass carried within the single, oversized mitochondrion possessed by each of these cells. This subgroup includes several parasites, collectively called trypanosomes, which cause devastating human diseases by infecting an insect species during a portion of their life cycle. *T. brucei* develops in the gut of the tsetse fly after the fly bites an infected human or other mammalian host. The parasite then travels to the insect salivary glands to be transmitted to another human or other mammal when the infected tsetse fly consumes another blood meal. *T. brucei* is common in central Africa and is the causative agent of African sleeping sickness, a disease associated with severe chronic fatigue and coma; it can be fatal if left untreated.

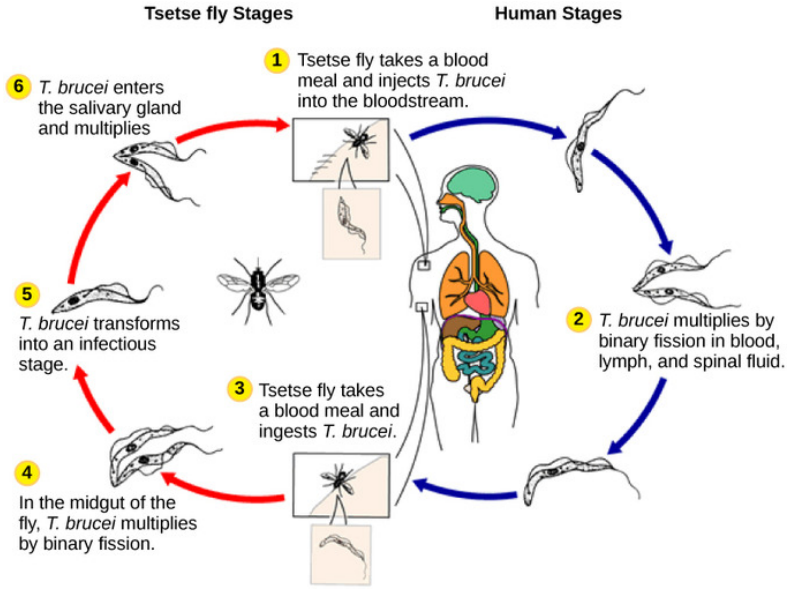

Figure: **Life cycle of *Trypanosoma brucei***: *Trypanosoma brucei*, the causative agent of sleeping sickness, spends part of its life cycle in the tsetse fly and part in humans.

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8.18C: Chromalveolata: Alveolates

Alveolates are defined by the presence of an alveolus beneath the cell membrane and include dinoflagellates, apicomplexans and ciliates.

Learning Objectives

- Evaluate traits associated with protists classified as alveolates which include dinoflagellates, apicomplexans, and ciliates

Key Points

- Alveolates are classified under the group Chromalveolata which developed as a result of a secondary endosymbiotic event.
- Dinoflagellates are defined by their flagella structure which lays perpendicular and fits into the cellulose plates of the dinoflagellate, promoting a spinning motion.
- Apicomplexans are defined by the asymmetrical distribution of their microtubules, fibrin, and vacuoles; they include the parasitic protist *Plasmodium* which causes malaria.
- Ciliates are defined by the presence of cilia (such as the oral groove in the *Paramecium)*, which beat synchronously to aid the organism in locomotion and obtaining nutrients.
- Ciliates are defined by the presence of cilia, which beat synchronously, to aid the organism in locomotion and obtaining nutrients, such as the oral groove in the *Paramecium*.

Key Terms

- **osmoregulation**: the homeostatic regulation of osmotic pressure in the body in order to maintain a constant water content
- **plastid**: any of various organelles found in the cells of plants and algae, often concerned with photosynthesis
- **conjugation**: the temporary fusion of organisms, especially as part of sexual reproduction

Chromalveolata

Current evidence suggests that species classified as chromalveolates are derived from a common ancestor that engulfed a photosynthetic red algal cell, which itself had already evolved chloroplasts from an endosymbiotic relationship with a photosynthetic prokaryote. Therefore, the ancestor of chromalveolates is believed to have resulted from a secondary endosymbiotic event. However, some chromalveolates appear to have lost red alga-derived plastid organelles or lack plastid genes altogether. Therefore, this supergroup should be considered a hypothesis-based working group that is subject to change and can be subdivided into alveolates and stramenopiles.

Alveolates

A large body of data supports that the alveolates are derived from a shared common ancestor. The alveolates are named for the presence of an alveolus, or membrane-enclosed sac, beneath the cell membrane. The exact function of the alveolus is unknown, but it may be involved in osmoregulation. The alveolates are further categorized into the dinoflagellates, the apicomplexans, and the ciliates.

Dinoflagellates

Dinoflagellates exhibit extensive morphological diversity and can be photosynthetic, heterotrophic, or mixotrophic. Many dinoflagellates are encased in interlocking plates of cellulose with two perpendicular flagella that fit into the grooves between the cellulose plates. One flagellum extends longitudinally and a second encircles the dinoflagellate. Together, the flagella contribute to the characteristic spinning motion of dinoflagellates. These protists exist in freshwater and marine habitats; they are a component of plankton.

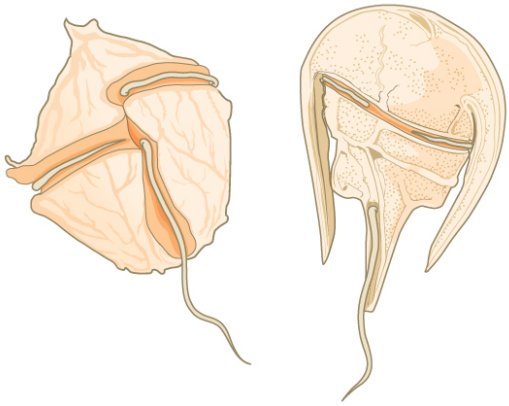

Figure: **Dinoflagellates**: The dinoflagellates exhibit great diversity in shape. Many are encased in cellulose armor and have two flagella that fit in grooves between the plates. Movement of these two perpendicular flagella causes a spinning motion.

Some dinoflagellates generate light, called bioluminescence, when they are jarred or stressed. Large numbers of marine dinoflagellates (billions or trillions of cells per wave) can emit light and cause an entire breaking wave to twinkle or take on a brilliant blue color. For approximately 20 species of marine dinoflagellates, population explosions (called blooms) during the summer months can tint the ocean with a muddy red color. This phenomenon is called a red tide and results from the abundant red pigments present in dinoflagellate plastids. In large quantities, these dinoflagellate species secrete an asphyxiating toxin that can kill fish, birds, and marine mammals. Red tides can be massively detrimental to commercial fisheries; humans who consume these protists may become poisoned.



Figure: **Bioluminescence**: Bioluminescence is emitted from dinoflagellates in a breaking wave, as seen from the New Jersey coast.

Apicomplexans

The apicomplexan protists are so named because their microtubules, fibrin, and vacuoles are asymmetrically distributed at one end of the cell in a structure called an apical complex. The apical complex is specialized for entry and infection of host cells. Indeed, all apicomplexans are parasitic. This group includes the genus *Plasmodium*, which causes malaria in humans. Apicomplexan life cycles are complex, involving multiple hosts and stages of sexual and asexual reproduction.

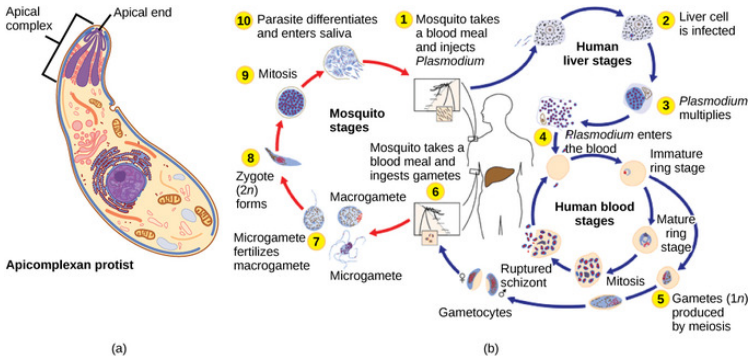

Figure: **Parasitic apicomplexans**: (a) Apicomplexans are parasitic protists. They have a characteristic apical complex that enables them to infect host cells. (b) Plasmodium, the causative agent of malaria, has a complex life cycle typical of apicomplexans.

Ciliates

The ciliates, which include *Paramecium* and *Tetrahymena*, are a group of protists 10 to 3,000 micrometers in length that are covered in rows, tufts, or spirals of tiny cilia. By beating their cilia synchronously or in waves, ciliates can coordinate directed movements and ingest food particles. Certain ciliates have fused cilia-based structures that function like paddles, funnels, or fins. Ciliates also are surrounded by a pellicle, providing protection without compromising agility. The genus *Paramecium*includes protists that have organized their cilia into a plate-like primitive mouth called an oral groove, which is used to capture and digest bacteria. Food captured in the oral groove enters a food vacuole where it combines with digestive enzymes. Waste particles are expelled by an exocytic vesicle that fuses at a specific region on the cell membrane: the anal pore. In addition to a vacuole-based digestive system, *Paramecium* also uses contractile vacuoles: osmoregulatory vesicles that fill with water as it enters the cell by osmosis and then contract to squeeze water from the cell.

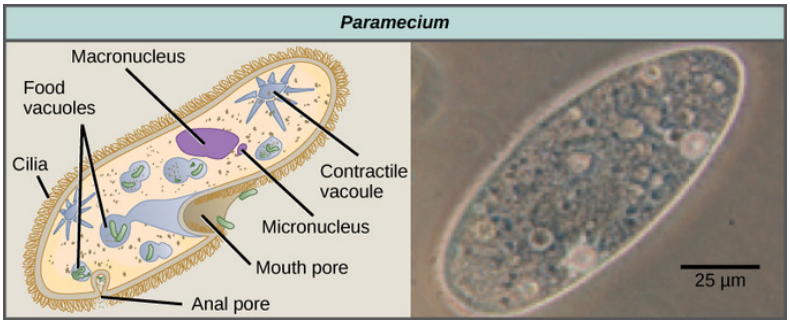

Figure: **Paramecium**: Paramecium has a primitive mouth (called an oral groove) to ingest food and an anal pore to excrete it. Contractile vacuoles allow the organism to excrete excess water. Cilia enable the organism to move.

Paramecium has two nuclei, a macronucleus and a micronucleus, in each cell. The micronucleus is essential for sexual reproduction, whereas the macronucleus directs asexual binary fission and all other biological functions. The process of sexual reproduction in *Paramecium* underscores the importance of the micronucleus to these protists. *Paramecium* and most other ciliates reproduce sexually by conjugation. This process begins when two different mating types of *Paramecium* make physical contact and join with a cytoplasmic bridge. The diploid micronucleus in each cell then undergoes meiosis to produce four haploid micronuclei. Three of these degenerate in each cell, leaving one micronucleus that then undergoes mitosis, generating two haploid micronuclei. The cells each exchange one of these haploid nuclei and move away from each other. A similar process occurs in bacteria that have plasmids. Fusion of the haploid micronuclei generates a completely novel diploid pre-micronucleus in each conjugative cell. This pre-micronucleus undergoes three rounds of mitosis to produce eight copies, while the original macronucleus disintegrates. Four of the eight pre-micronuclei become full-fledged micronuclei, whereas the other four perform multiple rounds of DNA replication and then become new macronuclei. Two cell divisions then yield four new paramecia from each original conjugative cell.

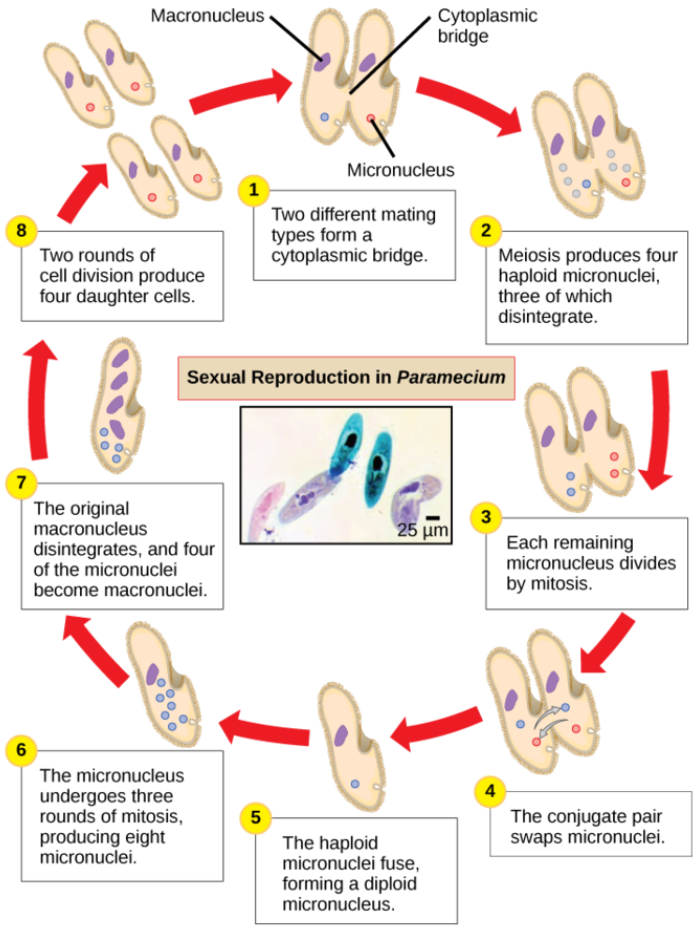

Figure: ***Paramecium*: sexual reproduction**: The complex process of sexual reproduction in *Paramecium* creates eight daughter cells from two original cells. Each cell has a macronucleus and a micronucleus. During sexual reproduction, the macronucleus dissolves and is replaced by a micronucleus.

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8.18D: Chromalveolata: Stramenopiles

Stramenophiles include photosynthetic marine algae and heterotrophic protists such as diatoms, brown and golden algae, and oomycetes.

Learning Objectives

- Describe characteristics of the following Stramenophiles: diatoms, brown algae, golden algae, and oomycetes

Key Points

- Stramenophiles, also referred to as heterokonts, are a subclass of chromalveolata, and are identified by the presence of a “hairy” flagellum.
- Diatoms, present in both freshwater and marine plankton, are unicellular photosynthetic protists that are characterized by the presence of a cell wall composed of silicon dioxide that displays intricate patterns.
- Golden algae, present in both freshwater and marine plankton communities, are unicellular photosynthetic protists characterized by the presence of carotenoids (yellow-orange photosynthetic pigments).
- Oomycetes, commonly referred to as water molds, are characterized by their fungus-like morphology, a cellulose-based cell wall, and a filamentous network used for nutrient uptake.
- Oomycetes, commonly referred to as water molds, are characterized by their fungus-like morphology, a cellulose-based cell wall and a filamentous network used for nutrient uptake.

Key Terms

- **stipe**: the stem of a kelp
- **raphe**: a ridge or seam on an organ, bodily tissue, or other structure, especially at the join between two halves or sections
- **saprobe**: an organism that lives off of dead or decaying organic material

Chromalveolates

Current evidence suggests that chromalveolates have an ancestor which resulted from a secondary endosymbiotic event. The species which fall under the classification of chromalveolates have evolved from a common ancestor that engulfed a photosynthetic red algal cell. This red algal cell had previously evolved chloroplasts from an endosymbiotic relationship with a photosynthetic prokaryote. Chromalveolates include very important photosynthetic organisms, such as diatoms, brown algae, and significant disease agents in animals and plants. The chromalveolates can be subdivided into alveolates and stramenopiles.

Stramenopiles

A subgroup of chromalveolates, the stramenopiles, also referred to as heterokonts, includes photosynthetic marine algae and heterotrophic protists. The unifying feature of this group is the presence of a textured, or “hairy,” flagellum. Many stramenopiles also have an additional flagellum that lacks hair-like projections. Members of this subgroup range in size from single-celled diatoms to the massive and multicellular kelp.

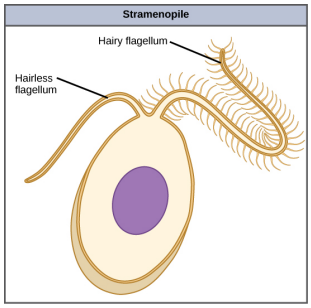

Figure: **Stramenophile structure**: This stramenopile cell has a single hairy flagellum and a secondary smooth flagellum.

Diatoms

The diatoms are unicellular photosynthetic protists that encase themselves in intricately patterned, glassy cell walls composed of silicon dioxide in a matrix of organic particles. These protists are a component of freshwater and marine plankton. Most species of

diatoms reproduce asexually, although some instances of sexual reproduction and sporulation also exist. Some diatoms exhibit a slit in their silica shell called a raphe. By expelling a stream of mucopolysaccharides from the raphe, the diatom can attach to surfaces or propel itself in one direction.

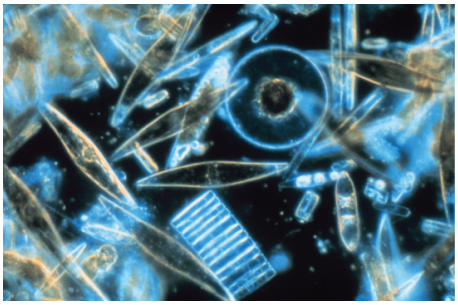

Figure: **Diatoms**: Assorted diatoms, visualized here using light microscopy, live among annual sea ice in McMurdo Sound, Antarctica. Diatoms range in size from 2 to 200 µm.

During periods of nutrient availability, diatom populations bloom to numbers greater than can be consumed by aquatic organisms. The excess diatoms die and sink to the sea floor where they are not easily reached by saprobes that feed on dead organisms. As a result, the carbon dioxide that the diatoms had consumed and incorporated into their cells during photosynthesis is not returned to the atmosphere. In general, this process by which carbon is transported deep into the ocean is described as the biological carbon pump because carbon is “pumped” to the ocean depths where it is inaccessible to the atmosphere as carbon dioxide. The biological carbon pump is a crucial component of the carbon cycle that helps to maintain lower atmospheric carbon dioxide levels.

Golden Algae

Like diatoms, golden algae are largely unicellular, although some species can form large colonies. Their characteristic gold color results from their extensive use of carotenoids, a group of photosynthetic pigments that are generally yellow or orange in color. Golden algae are found in both freshwater and marine environments, where they form a major part of the plankton community.

Brown Algae

The brown algae are primarily marine, multicellular organisms that are known colloquially as seaweeds. Giant kelps are a type of brown algae. Some brown algae have evolved specialized tissues that resemble terrestrial plants, with root-like holdfasts, stem-like stipes, and leaf-like blades that are capable of photosynthesis. The stipes of giant kelps are enormous, extending in some cases for 60 meters. A variety of algal life cycles exists, but the most complex is alternation of generations in which both haploid and diploid stages involve multicellularity. For instance, compare this life cycle to that of humans. In humans, haploid gametes produced by meiosis (sperm and egg) combine in fertilization to generate a diploid zygote that undergoes many rounds of mitosis to produce a multicellular embryo and then a fetus. However, the individual sperm and egg themselves never become multicellular beings. In the brown algae genus *Laminaria*, haploid spores develop into multicellular gametophytes, which produce haploid gametes that combine to produce diploid organisms that then become multicellular organisms with a different structure from the haploid form. Terrestrial plants also have evolved alternation of generations.

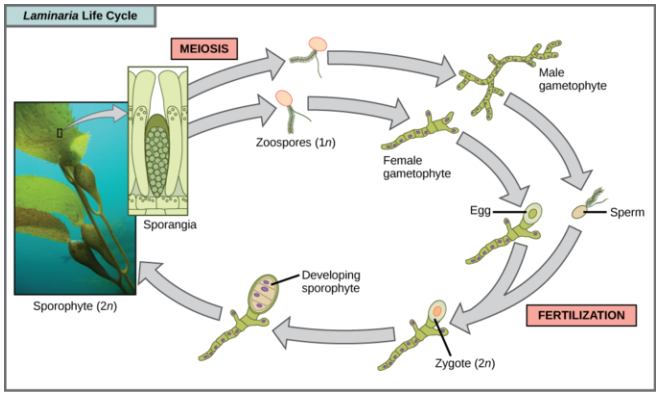

Figure: **Brown algae life cycle**: Several species of brown algae, such as the *Laminaria* shown here, have evolved life cycles in which both the haploid (gametophyte) and diploid (sporophyte) forms are multicellular. The gametophyte is different in structure from the sporophyte.

Oomycetes

The water molds, oomycetes (“egg fungus”), were so-named based on their fungus-like morphology, but molecular data have shown that the water molds are not closely related to fungi. The oomycetes are characterized by a cellulose-based cell wall and an extensive network of filaments that allow for nutrient uptake. As diploid spores, many oomycetes have two oppositely-directed flagella (one hairy and one smooth) for locomotion. The oomycetes are non-photosynthetic and include many saprobes and parasites. The saprobes appear as white fluffy growths on dead organisms. Most oomycetes are aquatic, but some parasitize terrestrial plants. One plant pathogen is *Phytophthora infestans*, the causative agent of late blight of potatoes, such as occurred in the nineteenth century Irish potato famine.



Figure: **Oomycete**: A saprobic oomycete engulfs a dead insect.

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8.18E: Rhizaria

Rhizaria are a supergroup of protists, typically amoebas, that are characterized by the presence of needle-like pseudopodia.

Learning Objectives

- Describe characteristics associated with Rhizaria

Key Points

- The needle-like pseudopodia are used to carry out a process called cytoplasmic streaming which is a means of locomotion or distributing nutrients and oxygen.
- Two major subclassifications of Rhizaria include Forams and Radiolarians.
- Forams are characterized as unicellular heterotrophic protists that have porous shells, referred to as tests, which can contain photosynthetic algae that the foram can use as a nutrient source.
- Radiolarians are characterized by a glassy silica exterior that displays either bilateral or radial symmetry.

Key Terms

- **pseudopodia**: temporary projections of eukaryotic cells
- **test**: the external calciferous shell of a foram

Rhizaria

The Rhizaria supergroup includes many of the amoebas, most of which have threadlike or needle-like pseudopodia. Pseudopodia function to trap and engulf food particles and to direct movement in rhizarian protists. These pseudopods project outward from anywhere on the cell surface and can anchor to a substrate. The protist then transports its cytoplasm into the pseudopod, thereby moving the entire cell. This type of motion, called cytoplasmic streaming, is used by several diverse groups of protists as a means of locomotion or as a method to distribute nutrients and oxygen.

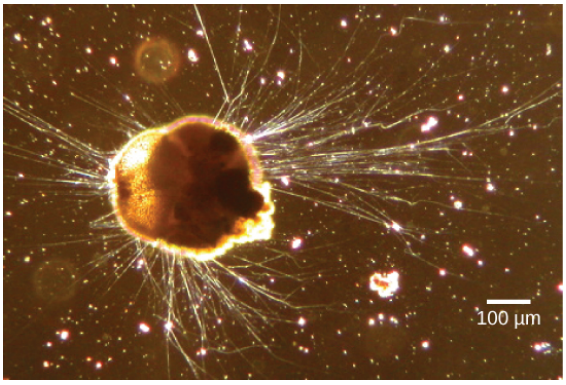

Figure: **Ammonia tepida**: Ammonia tepida, a Rhizaria species viewed here using phase contrast light microscopy, exhibits many threadlike pseudopodia.

Forams

Foraminiferans, or forams, are unicellular heterotrophic protists, ranging from approximately 20 micrometers to several centimeters in length; they occasionally resemble tiny snails. As a group, the forams exhibit porous shells, called tests, that are built from various organic materials and typically hardened with calcium carbonate. The tests may house photosynthetic algae, which the forams can harvest for nutrition. Foram pseudopodia extend through the pores and allow the forams to move, feed, and gather additional building materials. Foraminiferans are also useful as indicators of pollution and changes in global weather patterns.

The life-cycle involves an alternation between haploid and diploid phases. The haploid phase initially has a single nucleus, and divides to produce gametes with two flagella. The diploid phase is multinucleate, and after meiosis fragments to produce new organisms. The benthic forms has multiple rounds of asexual reproduction between sexual generations.

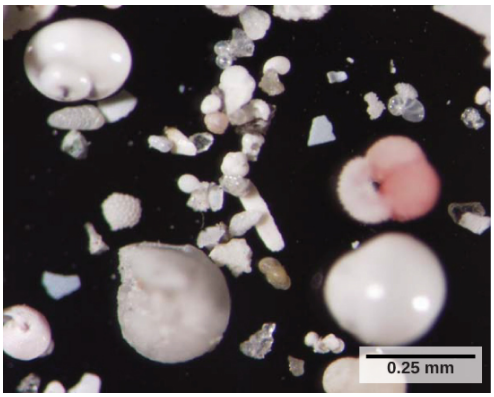

Figure: **Forams**: These shells from foraminifera sank to the sea floor.

Radiolarians

A second subtype of Rhizaria, the radiolarians, exhibit intricate exteriors of glassy silica with radial or bilateral symmetry. Radiolarians display needle-like pseudopods that are supported by microtubules which radiate outward from the cell bodies of these protists and function to catch food particles. The shells of dead radiolarians sink to the ocean floor, where they may accumulate in 100 meter-thick depths. Preserved, sedimented radiolarians are very common in the fossil record.

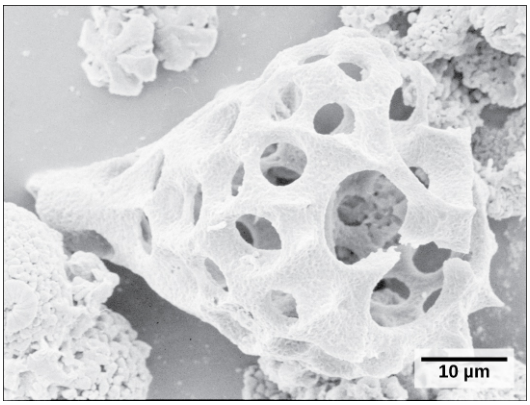

Figure: **Radiolarian shell**: This fossilized radiolarian shell was imaged using a scanning electron microscope.

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8.18F: Amoebozoa and Opisthokonta

Amoebozoa are a type of protist that is characterized by the presence of pseudopodia which they use for locomotion and feeding.

Learning Objectives

- Describe characteristics of Amoebozoa

Key Points

- Amoebozoa (amoebas) can live in either marine and fresh water or in soil.
- Amoebozoa are characterized by the presence of pseudopodia, which are extensions that can be either tube-like or flat lobes and are used for locomotion and feeding.
- Amooebozoa can be further divided into subclassifications that include slime molds; these can be found as both plasmodial and cellular types.
- Plasmodial slime molds are characterized by the presence of large, multinucleate cells that have the ability to glide along the surface and engulf food particles as they move.
- Cellular molds are characterized by the presence of independent amoeboid cells during times of nutrient abundancy and the development of a cellular mass, called a slug, during times of nutrient depletion.
- Archamoebae, Flabellinea, and Tubulinea are also groups of Amoebozoa; their defining characteristics include: Archamoebae lack mitochondria; Flabellinea flatten during locomotion and lack a shell and flagella; Tubulinea have a rough cylindrical form during locomotion with cylindrical pseudopodia.

Key Terms

- **rhizaria**: a species-rich supergroup of mostly unicellular eukaryotes that for the most part are amoeboids with filose, reticulose, or microtubule-supported pseudopods
- **plasmodium**: a mass of cytoplasm, containing many nuclei, created by the aggregation of amoeboid cells of slime molds during their vegetative phase
- **sporangia**: an enclosure in which spores are formed (also called a fruiting body)

Amoebozoa

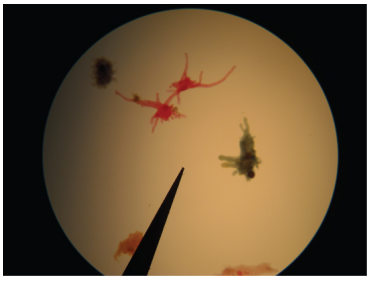

Figure: **Pseudopodia structures**: Amoebae with tubular and lobe-shaped pseudopodia, such as the ones seen under this microscope, would be morphologically classified as amoebozoans.

Protists are eukaryotic organisms that are classified as unicellular, colonial, or multicellular organisms that do not have specialized tissues. This identifying property sets protists apart from other organisms within the Eukarya domain. The amoebozoans are classified as protists with pseudopodia which are used in locomotion and feeding. Amoebozoans live in marine environments, fresh water, or in soil. In addition to the defining pseudopodia, they also lack a shell and do not have a fixed body. The pseudopodia which are characteristically exhibited include extensions which can be tube-like or flat lobes, rather than the hair-like pseudopodia of rhizarian amoeba. Rhizarian amoeba are amoeboids with filose, reticulose, or microtubule-supported pseudopods and include the groups: Cercozoa, Foraminifera, and Radiolaria and are classified as bikonts. The Amoebozoa include several groups of unicellular amoeba-like organisms that are free-living or parasites that are classified as unikonts. The best known and most well-studied member of this group is the slime mold. Additional members include the Archamoebae, Tubulinea, and Flabellinea.

Slime Molds



Figure: **Badhamia utricularis**: Badhamia utricularis: an example of a plasmodial slime mold with the ability to form a fruiting body.

A subset of the amoebozoans, the slime molds, has several morphological similarities to fungi that are thought to be the result of convergent evolution. For instance, during times of stress, some slime molds develop into spore -generating fruiting bodies, similar to fungi.

The slime molds are categorized on the basis of their life cycles into plasmodial or cellular types. Plasmodial slime molds are composed of large, multinucleate cells that move along surfaces like an amorphous blob of slime during their feeding stage. Food particles are lifted and engulfed into the slime mold as it glides along. Upon maturation, the plasmodium takes on a net-like appearance with the ability to form fruiting bodies, or sporangia, during times of stress. Haploid spores are produced by meiosis within the sporangia. These spores can be disseminated through the air or water to potentially land in more favorable environments. If this occurs, the spores germinate to form ameboid or flagellate haploid cells that can combine with each other and produce a diploid zygotic slime mold to complete the life cycle.



Figure: **Plasmodial slime mold: Physarum polycephalum**: Physarum polycephalum is an example of a cellular slime mold.

The cellular slime molds function as independent amoeboid cells when nutrients are abundant. When food is depleted, cellular slime molds pile onto each other into a mass of cells that behaves as a single unit called a slug. Some cells in the slug contribute to a 2–3-millimeter stalk, drying up and dying in the process. Cells atop the stalk form an asexual fruiting body that contains haploid spores. As with plasmodial slime molds, the spores are disseminated and can germinate if they land in a moist environment. One representative genus of the cellular slime molds is Dictyostelium, which commonly exists in the damp soil of forests.

Archamoebae, Flabellinea, and Tubulinea

The Archamoebae are a group of Amoebozoa distinguished by the absence of mitochondria. They include genera that are internal parasites or commensals of animals (*Entamoeba* and *Endolimax*). A few species are human pathogens, causing diseases such as amoebic dysentery. The other genera of archamoebae live in freshwater habitats and are unusual among amoebae in possessing flagella. Most have a single nucleus and flagellum, but the giant amoeba, *Pelomyxa*, has many of each.

The Tubulinea are a major grouping of Amoebozoa, including most of the larger and more familiar amoebae like *Amoeba*, *Arcella*, and *Difflugia*. During locomotion, most Tubulinea have a roughly cylindrical form or produce numerous cylindrical pseudopods. Each cylinder advances by a single central stream of cytoplasm, granular in appearance, and has no subpseudopodia. This distinguishes them from other amoeboid groups, although in some members this is not the normal type of locomotion.

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SECTION OVERVIEW

8.19: Algae

Topic hierarchy

8.19A: Archaeplastida

8.19B: Protists as Primary Producers, Food Sources, and Symbionts

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8.19A: Archaeplastida

Learning Objectives

- Describe the relationship between red algae, green algae, and land plants

Red algae and green algae are included in the supergroup Archaeplastida. It is well documented that land plants evolved from a common ancestor of these protists; their closest relatives are found within this group. Molecular evidence supports that all Archaeplastida are descendants of an endosymbiotic relationship between a heterotrophic protist and a cyanobacterium. The red and green algae include unicellular, multicellular, and colonial forms

Red Algae

Red algae, or rhodophytes, are primarily multicellular, lack flagella, and range in size from microscopic, unicellular protists to large, multicellular forms grouped into the informal seaweed category. The red algae life cycle is an alternation of generations. Some species of red algae contain phycoerythrins, photosynthetic accessory pigments that are red in color and outcompete the green tint of chlorophyll, making these species appear as varying shades of red. Other protists classified as red algae lack phycoerythrins and are parasites. Red algae are common in tropical waters where they have been detected at depths of 260 meters. Other red algae exist in terrestrial or freshwater environments.

Green Algae: Chlorophytes and Charophytes

The most abundant group of algae is the green algae. The green algae exhibit similar features to the land plants, particularly in terms of chloroplast structure. It is well supported that this group of protists share a relatively-recent common ancestors with land plants. The green algae are subdivided into the chlorophytes and the charophytes. The charophytes are the closest-living relatives of land plants, resembling them in morphology and reproductive strategies. Charophytes are common in wet habitats where their presence often signals a healthy ecosystem.

The chlorophytes exhibit great diversity of form and function. Chlorophytes primarily inhabit freshwater and damp soil; they are a common component of plankton. *Chlamydomonas* is a simple, unicellular chlorophyte with a pear-shaped morphology and two opposing, anterior flagella that guide this protist toward light sensed by its eyespot. More complex chlorophyte species exhibit haploid gametes and spores that resemble *Chlamydomonas*.

The chlorophyte *Volvox* is one of only a few examples of a colonial organism, which behaves in some ways like a collection of individual cells, but in other ways like the specialized cells of a multicellular organism. Volvox colonies contain 500 to 60,000 cells, each with two flagella, contained within a hollow, spherical matrix composed of a gelatinous glycoprotein secretion. Individual *Volvox* cells move in a coordinated fashion and are interconnected by cytoplasmic bridges. Only a few of the cells reproduce to create daughter colonies, an example of basic cell specialization in this organism.

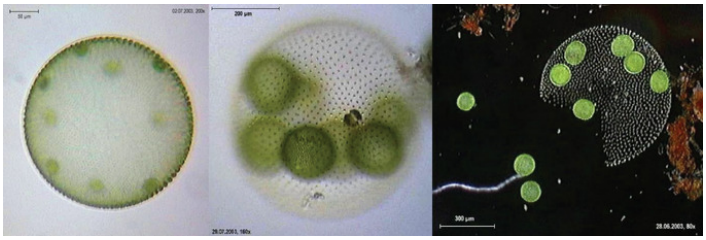

Figure: ***Volvox aureus:*** *Volvox aureus is a green alga in the supergroup Archaeplastida. This species exists as a colony, consisting of cells immersed in a gel-like matrix and intertwined with each other via hair-like cytoplasmic extensions.*

True multicellular organisms, such as the sea lettuce, *Ulva*, are represented among the chlorophytes. In addition, some chlorophytes exist as large, multinucleate, single cells. Species in the genus *Caulerpa*exhibit flattened, fern-like foliage and can reach lengths of 3 meters. *Caulerpa* species undergo nuclear division, but their cells do not complete cytokinesis, remaining instead as massive and elaborate single cells.



Figure: ***Caulerpa taxifolia****: Caulerpa taxifolia is a chlorophyte consisting of a single cell containing potentially thousands of nuclei.*

Key Points

- Archaeplastida are typically associated with their relationship to land plants; in addition, molecular evidence shows that Archaeplastida evolved from an endosymbiotic relationship between a heterotrophic protist and a cyanobacterium.
- Red algae (rhodophytes), are classified as Archaeplastida and are most often characterized by the presence of the red pigment phycoerythrin; however, there are red algae that lack phycoerythrins and can be classified as parasites.
- Red algae typically exist as multicellular protists that lack flagella; however, they can also exist as unicellular organisms.
- Green algae are the most abundant group of algae and can be further classified as chlorophytes and charophytes.
- Charophytes are the green algae which resemble land plants and are their closest living relative.
- Chlorophytes are the green algae which exhibit a wide range of forms; they can be unicellular, multicellular, or colonial.

Key Terms

- **endosymbiotic**: that lives within a body or cells of another organism
- **plankton**: a generic term for all the organisms that float in the sea

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8.19B: Protists as Primary Producers, Food Sources, and Symbionts

Protists function as sources of food for organisms on land and sea.

Learning Objectives

- Give examples of how protists act as primary producers

Key Points

- Photosynthetic protists serve as producers of nutrition for other organisms.
- Protists like zooxanthellae have a symbiotic relationship with coral reefs; the protists act as a food source for coral and the coral provides shelter and compounds for photosynthesis for the protists.
- Protists feed a large portion of the world's aquatic species and conduct a quarter of the world's photosynthesis.
- Protists help land-dwelling animals such as cockroaches and termites digest cellulose.

Key Terms

- **zooxanthella**: an animal of the genus Symbiodinium, a yellow dinoflagellate, notably found in coral reefs
- **primary producer**: an autotroph organism that produces complex organic matter using photosynthesis or chemosynthesis

Primary Producers/Food Sources

Protists function in various ecological niches. Some protist species are essential components of the food chain and are generators of biomass.

Protists are essential sources of nutrition for many other organisms. In some cases, as in plankton, protists are consumed directly. Alternatively, photosynthetic protists serve as producers of nutrition for other organisms. For instance, photosynthetic dinoflagellates called zooxanthellae use sunlight to fix inorganic carbon. In this symbiotic relationship, these protists provide nutrients for the coral polyps that house them, giving corals a boost of energy to secrete a calcium carbonate skeleton. In turn, the corals provide the protists with a protected environment and the compounds needed for photosynthesis. This type of symbiotic relationship is important in nutrient-poor environments. Without dinoflagellate symbionts, corals lose algal pigments in a process called coral bleaching and they eventually die. This explains why reef-building corals do not reside in waters deeper than 20 meters: insufficient light reaches those depths for dinoflagellates to photosynthesize.



Figure: **Corals and dinoflagellates**: Coral polyps obtain nutrition through a symbiotic relationship with dinoflagellates.

The protists themselves and their products of photosynthesis are essential, directly or indirectly, to the survival of organisms ranging from bacteria to mammals. As primary producers, protists feed a large proportion of the world's aquatic species. (On land, terrestrial plants serve as primary producers.) In fact, approximately one-quarter of the world's photosynthesis is conducted by protists, particularly dinoflagellates, diatoms, and multicellular algae.



Figure: **Protists and aquatic organisms**: Virtually all aquatic organisms depend directly or indirectly on protists for food.

Protists do not only create food sources for sea-dwelling organisms. Certain anaerobic parabasalid species exist in the digestive tracts of termites and wood-eating cockroaches where they contribute an essential step in the digestion of cellulose ingested by these insects as they bore through wood.

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SECTION OVERVIEW

8.20: Helminths

Topic hierarchy

8.20A: Characteristics of Helminths

8.20B: Classification and Identification of Helminths

8.20C: Distribution and Importance of Parasitic Worms

8.20D: Arthropods as Vectors

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8.20A: Characteristics of Helminths

Learning Objectives

- Describe the attributes of helminths

Parasitic worms that inhabit the intestinal tract (blood, tissue and organs) of humans are referred to as helminths. They receive nourishment and protection by living within the host where they cause disease. The parasitic intestinal helminths can be divided into three groups which include Nematodes (roundworms), Cestodes (tapeworms), and Trematodes (flukes). Helminths share numerous characteristics that contribute to their parasitic quality including the presence of attachment organs. These attachment organs include bothria (sucking grooves: Cestodes or tapeworms, which may also have a rostellum (crown of thorns with hooks); Old World Hookworms: cutting teeth; New World Hookworms: cutting plate. These attachment organs allow these particular helminths to reside within their human host. It should be noted, however, that blood and tissue roundworms (Nematodes) exist that will not be discussed in this section.

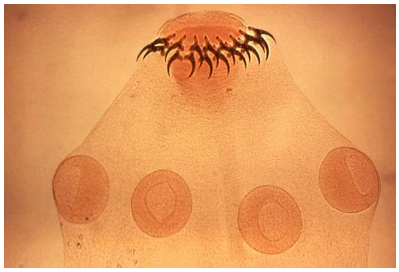

Figure: ***Suckers on Taenia solium****: A micrograph showing the morphology of a Taenia solium tapeworm scolex with its four suckers, and two rows of hooks.*

The three commonly studied and well-known groups include the intestinal Nematodes (round worms), tapeworms (Cestodes), and blood, tissue and organ flukes (Trematodes). Intestinal helminths are commonly transmitted through fecally contaminated food and water and these parasites include *Ascaris lumbricoides*, *Trichuris trichiura* (whipworm), and *Enterobius vermicularis* (pinworm).

Hookworms include Ancylostoma duodenale and Necator americanus, whose larvae penetrate the skin after their ova have been passed in human feces. These soil-transmitted helminths are associated with climates that are warm and moist and where sanitation and hygiene are poor. The eggs are passed in the feces of the infected individual, the larvae hatch, contaminate the soil, and can penetrate the skin when contact is made.



Figure: ***Hookworms****: An image of a hookworm attached to intestinal mucosa.*

Ascaris lumbricoides, the cause of Ascariasis, is a type of soil transmitted helminth. Ascaris, the largest roundworm, lives in the intestine and the eggs are passed in the feces of the infected person. Ascariasis is caused by ingestion of eggs from food and water contaminated with feces from humans infected with Ascaris, and ingestion allows for continuation of the life cycle. Ascariasis may not be symptomatic, but may become symptomatic or fatal if intestinal blockage occurs without surgical intervention.

Hookworms, another type of soil-transmitted helminth, reside in the small intestine and eggs are passed in the feces of the infected individual. The eggs will mature and hatch in the soil and the immature worms (larvae) will penetrate the skin of humans if contact is made. The hookworm is transmitted by exposing bare skin to contaminated soil.

Whipworms (Trichuris trichiura), a type of soil-transmitted helminth, resides in the large intestine and eggs are passed in the feces of the infected individuals. The eggs will mature into an infective form in the soil and transmission occurs by ingestion of eggs in fecally contaminated food and water. Individuals with whipworm may have light or heavy infections. Light infections are usually

not significantly symptomatic. However, heavy symptoms include frequent, painful passage of stool that contains mucus, water, and blood.

This summary does not contain an exhaustive compilation of all human parasitic nematodes, but merely a representation of several species.

Key Points

- Helminths can cause disruption of the hosts nutrient absorption by utilizing all nutrients that pass through the intestinal tract.
- There are four major groups of parasitic worms: monogeneans, cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes).
- Helminths are characterized by the presence of attachment organs which include suckers, hooks, lips, teeth, and dentary plates.

Key Terms

- **parasitic worm**: Parasitic worms are referred to helminths as they live and feed on living hosts. Helminths receive both nourishment and protection by disrupting the hosts ability to absorb nutrients resulting in weakness and disease of the host.
- **bothridia**: A sucker or attachment organ on a parasitic worm.
- **helminth**: A parasitic roundworm or flatworm.

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8.20B: Classification and Identification of Helminths

Helminths, or parasitic worms, are eukaryotic parasites characterized by their ability to feed and live on living hosts.

Learning Objectives

- Recall the attributes of helminths

Key Points

- The major groups of parasitic helminths include: platyhelminths (flatworms), acanthocephalins (thorny-headed worms) cestodes (tapeworms), trematodes (flukes) and nematodes (roundworms).
- The classification and identification of helminths are dependent on numerous factors including body shape, body cavity, body covering, digestive tubing, sex and type of attachment organs.
- Parasitic worms disrupt the ability of a host to receive and obtain nourishment.

Key Terms

- **acetabulum**: A large posterior sucker, for example that of leeches.
- **tegument**: A natural covering of the body or of a bodily organ.
- **bothridia**: A sucker or attachment organ on a parasitic worm.

Helminthsare large, multicellular organisms that are visible to the eye once in the adult stage of their life cycle. Helminths and multicellular eukaryotes, can either be free-living or parasitic.

In their adult form, helminths are unable to multiply in humans and utilize numerous mechanisms of transmission to ensure reproductive success. These parasites live in and feed on hosts which allow them to obtain nourishment while disrupting the hosts' nutrient absorption. Parasitic worms are commonly found within the intestine and thus, are called intestinal parasites. They are able to live in both humans and animals.

The major groups of parasitic helminths include:

- *platyhelminths* (flatworms)
- *acanthocephalins* (thorny-headed worms)
- *cestodes* (tapeworms)
- *trematodes* (flukes)
- *nematodes* (roundworms).



Figure: **Helminths**: Image of a tapeworm, specifically an adult Ascaris lumbriocoides worm.

The classification and identification of helminths are dependent on numerous factors including body shape, body cavity, body covering, digestive tubing, sex and type of attachment organs.

Platyhelminths (flatworms) include both trematodes (flukes) and cestodes (tapeworms). Specifically, tapeworms are characterized using the above criteria and are organized in a segmented plane. They lack a body cavity and have a *tegument* body covering. Tapeworms lack a digestive tube and are hermaphroditic. They utilize suckers or *bothridia*, and *rostellum* with hooks for an attachment organ.

Trematodes are characterized by an unsegmented plane for body shape. They also lack a body cavity and have a tegument for body covering. However, the digestive tube for trematodes ends in the cecum. Trematodes are hermaphroditic and utilize oral suckers, ventral suckers or *acetabulum* for attachment organs.

Nematodes are characterized by a cylindrical body shape and do indeed have a body cavity. Its body covering is a cuticle and the digestive tube ends in the anus. The sex of nematodes is *dioecious* (distinct male and female organisms). Lastly, their attachment organs range from lips, teeth, filariform extremities and dentary plates.

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8.20C: Distribution and Importance of Parasitic Worms

Parasitic worms, distributed worldwide, are hypothesized to have importance in immune system regulation.

Learning Objectives

- Explain how parasitic worms may be beneficial

Key Points

- Parasitic worms appear to have medicinal properties as well which has opened a new field of research by studying the use of parasitic worms in disease treatment.
- Scientists hypothesize that parasitic worms can be used to combat autoimmune diseases by damping down the immune system of the host by using parasitic worms to active eosinophils and downstream targets.
- Parasitic worms have been linked to a protective role in autoimmune disease development and prevention of metabolic syndrome.

Key Terms

- **eosinophils**: a type of white blood cell used to fight parasitic infection



Figure: **Image of Necator Americanus**: Infectious Necator americanus larva are applied to the skin in therapy, either in a single dose or in multiple smaller doses over the course of two or three months.

Parasitic worms, often the result of horrible illness and disease, appear to have medicinal properties as well. The importance of parasitic worms has come to light in regards to treating various diseases which may benefit from their presence. It is argued that humans have evolved with parasitic worms and there is a mutualistic relationship which mandates the need for parasitic worms to contribute to a healthy immune system. The most common use of parasitic worms for medicinal purposes is in the use against diseases characterized by an overactive immune response. An overactive immune response is often seen in individuals with allergies and hay-fever, specifically in developed countries where parasites have been under strict prevention and control. It is speculated that parasitic worms have the ability to damp down the immune system, which promotes an environment where they can thrive without being attached. In return, the damping down of the immune system is believed to be beneficial, as this may prevent the development of allergies.

An additional study links an increase in metabolic syndrome in the Western world and the success in preventing and eliminating parasites. The study demonstrates that immune system cells, eosinophils, that are present in fat tissue play a role in the prevention of insulin resistance via secretion of interleukin 4. The interleukin 4 is then able to activate macrophages that function in the maintenance of glucose homeostasis. The study showed that parasitic worm infection results in an increase in eosinophils, thus, promoting control of glucose maintenance.

The hypothesis that parasites are necessary for a healthy immune system is currently under investigation and still requires multiple lines of evidence.

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8.20D: Arthropods as Vectors

Arthropods are capable of functioning as vectors by transmitting diseases.

Learning Objectives

- Demonstrate how arthropods act as disease vectors

Key Points

- Arthropods will transmit diseases via their ability to function as hematophagous vectors which is characterized as their ability to feed on blood at some or all stages of their life cycles.
- Arthropod vectors include mosquitoes, fleas, sand flies, lice, fleas, ticks and mites.
- Arthropods transmit parasites either by injection into the blood stream of the host directly via their salivary glands, or by forcing parasites into a pool of blood which develops when chewing the skin.

Key Terms

- **vector**: A carrier of a disease-causing agent.
- **hematophagous**: feeding on blood

Arthropods are capable of serving as vectors, indicating that they play a major role in disease transmission. Arthropods that serve as vectors include mosquitoes, fleas, sand flies, lice, ticks, and mites. These arthropods are responsible for the transmission of numerous diseases. These types of vectors are considered to be hematophagous. These arthropod vectors are characterized as feeding on blood at some or all stages of their life cycles. The arthropods feed on the blood which typically allows parasites to enter the bloodstream of the host.

The Anopheles mosquito serves as a vector for malaria, filariasis, and arboviruses as well (arthropod-borne-viruses). The Anopheles mosquito inserts its mouthpart under the skin and feeds on the hosts. As the mosquito is feeding on the host blood, the parasites which are carried by the mosquito, are typically located within its salivary glands. The mosquito is able to directly transfer the parasites into the blood stream of the host. Pool feeders, which include both the sand and black fly, responsible for Leishmaniasis and Onchocerciasis diseases, will chew the hosts skin. The chewing action produces a well which promotes the formation of a small pool of blood from which they feed. In the case of sand flies, responsible for Leishmaniasis, the parasites infect the host through the saliva. In the case of black flies, responsible for Onchocerciasis, the parasites are forced out of the insects head into the pool of blood. Tsetse flies are vectors of the human African trypanosomiasis, called “African sleeping sickness”. Additional examples of mosquitoes include the Aedes mosquito which is a vector for avian malaria, dengue fever, and yellow fever.

Fleas are another type of arthropod vector that transmit numerous diseases. The human flea, Pulex irritans, and the Oriental rat flea, Xenopsylla cheopis, are responsible for the transmission of the bubonic plague, murine typhus, and tapeworms.

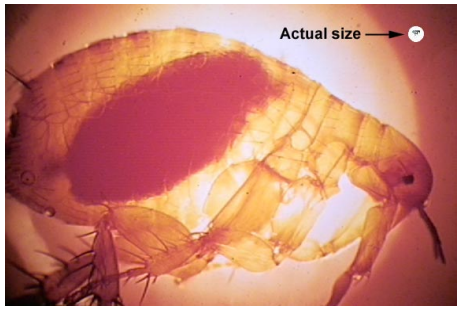

Figure: **Male Xenopsylla cheopis (oriental rat flea) engorged with blood.**: Image of Xenopsylla chepsis (oriental rat flea) engorged with blood. The oriental rat flea is an example of an arthropod vector as it is the primary vector of plague. This vector has been the cause of large plague epidemics in Asia, Africa, and South America. Both male and female fleas can transmit the infection.

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Thumbnail: This colorized transmission electron microscopic (TEM) image revealed some of the ultrastructural morphology displayed by an Ebola virus virion. (Public Domain; Frederick A. Murphy via CDC).

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SECTION OVERVIEW

9.1: Overview of Viruses

Topic hierarchy

9.1A: Discovery and Detection of Viruses

9.1B: Nature of the Virion

9.1C: Viral Genomes

9.1D: Host Range

9.1E: Viral Size

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9.1A: Discovery and Detection of Viruses

Viruses are infectious particles about 100 times smaller than bacteria and can only be observed by electron microscopy.

Learning Objectives

- Describe how viruses were first discovered and how they are detected

Key Points

- Virions, single virus particles, are 20–250 nanometers in diameter.
- In the past, viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether they had single- or double-stranded nucleic acid.
- Molecular analysis of viral replicative cycles is now more routinely used to classify viruses.

Key Terms

- **virus**: a submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat
- **virion**: a single individual particle of a virus (the viral equivalent of a cell)

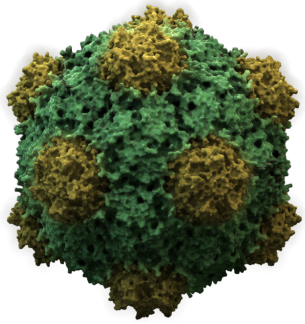

Figure: **The structure of the icosahedral cowpea mosaic virus**: In the past, viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether they had single- or double-stranded nucleic acid.

Discovery and Detection

Viruses were first discovered after the development of a porcelain filter, called the Chamberland-Pasteur filter, which could remove all bacteria visible in the microscope from any liquid sample. In 1886, Adolph Meyer demonstrated that a disease of tobacco plants, tobacco mosaic disease, could be transferred from a diseased plant to a healthy one via liquid plant extracts. In 1892, Dmitri Ivanowski showed that this disease could be transmitted in this way even after the Chamberland-Pasteur filter had removed all viable bacteria from the extract. Still, it was many years before it was proven that these “filterable” infectious agents were not simply very small bacteria, but were a new type of tiny, disease-causing particle.

Virions, single virus particles, are very small, about 20–250 nanometers in diameter. These individual virus particles are the infectious form of a virus outside the host cell. Unlike bacteria (which are about 100 times larger), we cannot see viruses with a light microscope, with the exception of some large virions of the poxvirus family. It was not until the development of the electron microscope in the late 1930s that scientists got their first good view of the structure of the tobacco mosaic virus (TMV) and other viruses. The surface structure of virions can be observed by both scanning and transmission electron microscopy, whereas the internal structures of the virus can only be observed in images from a transmission electron microscope. The use of these technologies has enabled the discovery of many viruses of all types of living organisms. They were initially grouped by shared morphology. Later, groups of viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether their nucleic acid was single- or double-stranded. More recently, molecular analysis of viral replicative cycles has further refined their classification.

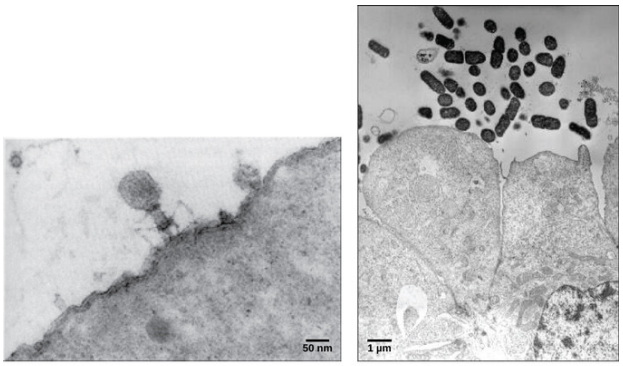

Figure: **Examples of transmission electron micrographs of viruses**: In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these E. coli cells are dwarfed by cultured colon cells.

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9.1B: Nature of the Virion

A virion is a complete viral particle consisting of RNA or DNA surrounded by a protein shell, constituting the infective form of a virus.

Learning Objectives

- Illustrate the attributes of a virion

Key Points

- The virion shell or capsid protects the interior core that includes the genome and other proteins. After the virion binds to the surface of a specific host cell, its DNA or RNA is injected into the host cell and viral replication occurs, resulting in the spread of the infection to other host cells.
- A virion is the infectious particle that is designed for transmitting the nucleic acid genome among hosts or host cells.
- Virions are produced in the cytoplasm of complex viral 'factories,' the virus.

Key Terms

- **capsid**: The outer protein shell of a virus.

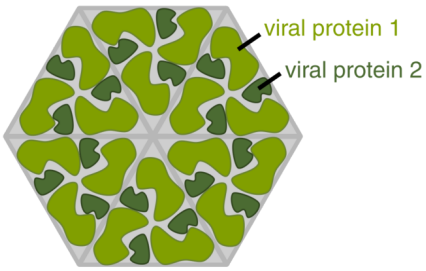

Figure: **Virion capsid**: Structure of a capsid and the organization of molecules that constitute it.

A virion is an entire virus particle consisting of an outer protein shell called a *capsid* and an inner core of nucleic acid (either ribonucleic or deoxyribonucleic acid—RNA or DNA). The core confers infectivity, and the capsid provides specificity to the virus. In some virions the capsid is further enveloped by a fatty membrane, in which case the virion can be inactivated by exposure to fat solvents such as ether and chloroform. Many virions are spheroidal—actually icosahedral (the capsid having 20 triangular faces)—with regularly arranged units called capsomeres, two to five or more along each side. The nucleic acid is densely coiled within. Other virions have a capsid consisting of an irregular number of surface spikes, with the nucleic acid loosely coiled within. Virions of most plant viruses are rod-shaped; the capsid is a naked cylinder (lacking a fatty membrane) within which lies a straight or helical rod of nucleic acid.

Virion capsids are formed from identical protein subunits called capsomeres. Viruses can have a lipid "envelope" derived from the host cell membrane. The capsid is made from proteins encoded by the viral genome and its shape serves as the basis for morphological distinction. Virally coded protein subunits will self-assemble to form a capsid, in general requiring the presence of the virus genome. Complex viruses code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The capsid and entire virus structure can be mechanically (physically) probed through atomic force microscopy.

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9.1C: Viral Genomes

Learning Objectives

- Generalize the features of viral genomes

Viral diseases have an enormous impact on human health worldwide. Genomic technologies are providing infectious disease researchers an unprecedented capability to study at a genetic level the viruses that cause disease and their interactions with infected hosts. An enormous variety of genomic structures can be seen among viral species; as a group, they contain more structural genomic diversity than plants, animals, archaea, or bacteria. There are millions of different types of viruses, although only about 5,000 of them have been described in detail.

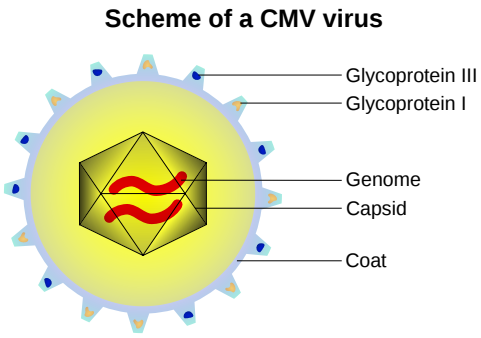

Figure: ***Diagram of a virus****: The location of the genome inside the virus.*

A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus, respectively. The vast majority of viruses have RNA genomes. Plant viruses tend to have single-stranded RNA genomes and bacteriophages tend to have double-stranded DNA genomes. Viral genomes are circular, as in the polyomaviruses, or linear, as in the adenoviruses. The type of nucleic acid is irrelevant to the shape of the genome. Among RNA viruses and certain DNA viruses, the genome is often divided up into separate parts, in which case it is called segmented. For RNA viruses, each segment often codes for only one protein, and they are usually found together in one capsid. However, all segments are not required to be in the same virion for the virus to be infectious, as demonstrated by the brome mosaic virus and several other plant viruses.

A viral genome, irrespective of nucleic acid type, is almost always either single-stranded or double-stranded. Single-stranded genomes consist of an unpaired nucleic acid, analogous to one-half of a ladder split down the middle. Double-stranded genomes consist of two complementary paired nucleic acids, analogous to a ladder. The virus particles of some virus families, such as those belonging to the Hepadnaviridae, contain a genome that is partially double-stranded and partially single-stranded.

Key Points

- In modern molecular biology and genetics, the genome is the entirety of an organism ‘s hereditary information. It is encoded either in DNA or, for many types of virus, in RNA.
- A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus.
- The genome includes both the genes and the non-coding sequences of the DNA/RNA.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

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9.1D: Host Range

A virus' host range is the range of cell types and host species a virus is able to infect.

Learning Objectives

- Explain factors that limit viral host range

Key Points

- The host range or host specificity of a parasite is the collection of hosts that an organism can use as a partner.
- The host range is usually a function of an inability of the virus to successfully adsorb and/or enter cells because of an incompatibility between virus capsid proteins (or virus envelope proteins) and the host receptor molecule.
- The host range is also a function of an incompatibility between the biochemistry of the virus and the biochemistry of the host. For closely related hosts, the biochemical differences can be quite subtle.

Key Terms

- **surface receptor**: Cell surface receptors (membrane receptors, transmembrane receptors) are specialized integral membrane proteins that take part in communication between the cell and the outside world.
- **commensal**: A term for a form of symbiosis in which one organism derives a benefit while the other is unaffected

Factors Limiting Viral Infection

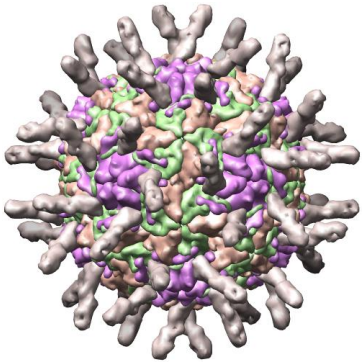

Figure: **ICAM-1**: structure of ICAM-1 molecule that enables viruses to bind to host's cell membrane.

A host is an organism that harbors a parasite or a mutual or commensal symbiont, typically providing nourishment and shelter. Resistance to and recovery from viral infections depend on the interactions that occur between the virus and the host. The defenses mounted by the host may act directly on the virus or indirectly on virus replication by altering or killing the infected cell. Non-specific host defenses function early in an encounter with a virus to prevent or limit infection, while the specific host defenses function after infection in recovery to provide immunity for subsequent challenges.

The host defense mechanisms involved in a particular viral infection will vary depending on the virus, dose, and portal of entry. The host has many barriers against infection that are inherent in the organism. These represent the first line of defense, which functions to prevent or limit infection Examples of natural barriers include but are not limited to skin, the expression of surface receptors such as CD4, complement receptors, glycophorin, intercelullar adhesion molecule 1 (ICAM-1), mucus, a ciliated epithelium, low pH, and humoral and cellular components.

The host range of the virus will depend upon the presence of the receptors described above. If a host lacks the receptor for a virus, or if the host cell lacks some component necessary for the replication of a virus, the host will inherently be resistant to that virus. For example, mice lack the receptors for polio viruses and thus are resistant to polio virus. Similarly, humans are inherently resistant to plant and many animal viruses.

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9.1E: Viral Size

Most viruses range in size from 5 to 300 nanometers (nm), although some Paramyxoviruses can be up to 14,000 nm long.

Learning Objectives

- Recognize the cause and effect of different sizes of viruses

Key Points

- The size and shape of a virus helps us understand its class and components.
- Viruses also exist in different shapes that include helical, polyhedral, enveloped, and complex.
- Proteins and nucleic acid of viruses determine their size and shape.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.

A virus is an infectious agent of small size and simple composition that can multiply only in living cells of animals, plants, or bacteria. They range in size from about 20 to 400 nanometres in diameter (1 nanometre = 10^{-9} meters). By contrast, the smallest bacteria are about 400 nanometres in size. A virus consists of a single- or double-stranded nucleic acid and at least one protein surrounded by a protein shell, called a capsid; some viruses also have an outer envelope composed of fatty materials (lipids) and proteins. The nucleic acid carries the virus's genome —its collection of genes—and may consist of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). The protein capsid provides protection for the nucleic acid and may contain enzymes that enable the virus to enter its appropriate host cell.

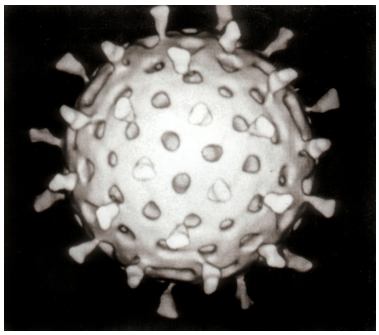

Figure: **Viral structure**: Rotavirus particles measure 76.5 nm in diameter and are not enveloped.

There exists a strong association between viral geometry and features of viral disease outbreaks. The amount and arrangement of the proteins and nucleic acid of viruses determine their size and shape. The protein and nucleic acid constituents have properties unique for each class of virus; when assembled, they determine the size and shape of the virus for that specific class.

Only the largest and most complex viruses can be seen under the light microscope at the highest resolution. Any determination of the size of a virus also must take into account its shape, since different classes of viruses have distinctive shapes. Shapes of viruses are predominantly of two kinds: rods, or filaments, so called because of the linear array of the nucleic acid and the protein subunits; and spheres, which are actually 20-sided (icosahedral) polygons. Most plant viruses are small and are either filaments or polygons, as are many bacterial viruses. The larger and more-complex bacteriophages contain double-stranded DNA as their genetic information and combine both filamentous and polygonal shapes. The classic T4 bacteriophage is composed of a polygonal head, which contains the DNA genome, and a special-function rod-shaped tail of long fibres. Structures such as these are unique to the bacteriophages.

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SECTION OVERVIEW

9.2: Structure of Viruses

Topic hierarchy

9.2A: Viral Morphology

9.2B: General Morphology

9.2C: Complex and Asymmetrical Virus Particles

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9.2A: Viral Morphology

Viruses of all shapes and sizes consist of a nucleic acid core, an outer protein coating or capsid, and sometimes an outer envelope.

Learning Objectives

- Describe the relationship between the viral genome, capsid, and envelope

Key Points

- Viruses are classified into four groups based on shape: filamentous, isometric (or icosahedral), enveloped, and head and tail.
- Many viruses attach to their host cells to facilitate penetration of the cell membrane, allowing their replication inside the cell.
- Non-enveloped viruses can be more resistant to changes in temperature, pH, and some disinfectants than are enveloped viruses.
- The virus core contains the small single- or double-stranded genome that encodes the proteins that the virus cannot get from the host cell.

Key Terms

- **capsid**: the outer protein shell of a virus
- **envelope**: an enclosing structure or cover, such as a membrane
- **filamentous**: Having the form of threads or filaments
- **isometric**: of, or being a geometric system of three equal axes lying at right angles to each other (especially in crystallography)

Viral Morphology

Viruses are acellular, meaning they are biological entities that do not have a cellular structure. Therefore, they lack most of the components of cells, such as organelles, ribosomes, and the plasma membrane. A virion consists of a nucleic acid core, an outer protein coating or capsid, and sometimes an outer envelope made of protein and phospholipid membranes derived from the host cell. The capsid is made up of protein subunits called capsomeres. Viruses may also contain additional proteins, such as enzymes. The most obvious difference between members of viral families is their morphology, which is quite diverse. An interesting feature of viral complexity is that host and virion complexity are uncorrelated. Some of the most intricate virion structures are observed in bacteriophages, viruses that infect the simplest living organisms: bacteria.

Morphology

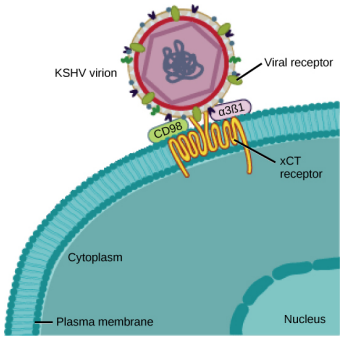

Figure: **Example of a virus attaching to its host cell**: The KSHV virus binds the xCT receptor on the surface of human cells. This attachment allows for later penetration of the cell membrane and replication inside the cell.

Viruses come in many shapes and sizes, but these are consistent and distinct for each viral family. In general, the shapes of viruses are classified into four groups: filamentous, isometric (or icosahedral), enveloped, and head and tail. Filamentous viruses are long and cylindrical. Many plant viruses are filamentous, including TMV (tobacco mosaic virus). Isometric viruses have shapes that are roughly spherical, such as poliovirus or herpesviruses. Enveloped viruses have membranes surrounding capsids. Animal viruses, such as HIV, are frequently enveloped. Head and tail viruses infect bacteria. They have a head that is similar to icosahedral viruses and a tail shape like filamentous viruses.

Many viruses use some sort of glycoprotein to attach to their host cells via molecules on the cell called viral receptors. For these viruses, attachment is a requirement for later penetration of the cell membrane, allowing them to complete their replication inside the cell. The receptors that viruses use are molecules that are normally found on cell surfaces and have their own physiological functions. Viruses have simply evolved to make use of these molecules for their own replication.

Overall, the shape of the virion and the presence or absence of an envelope tell us little about what disease the virus may cause or what species it might infect, but they are still useful means to begin viral classification. Among the most complex virions known, the T4 bacteriophage, which infects the *Escherichia coli* bacterium, has a tail structure that the virus uses to attach to host cells and a head structure that houses its DNA. Adenovirus, a non-enveloped animal virus that causes respiratory illnesses in humans, uses glycoprotein spikes protruding from its capsomeres to attach to host cells. Non-enveloped viruses also include those that cause polio (poliovirus), plantar warts (papillomavirus), and hepatitis A (hepatitis A virus).

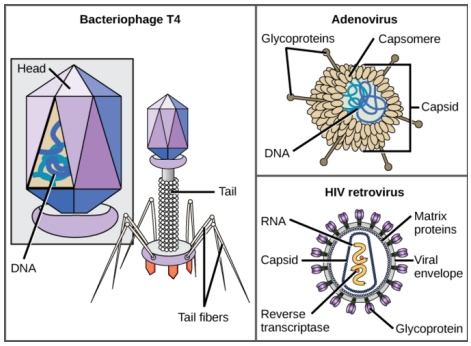

Figure: **Examples of virus shapes**: Viruses can be either complex in shape or relatively simple. This figure shows three relatively-complex virions: the bacteriophage T4, with its DNA-containing head group and tail fibers that attach to host cells; adenovirus, which uses spikes from its capsid to bind to host cells; and HIV, which uses glycoproteins embedded in its envelope to bind to host cells.

Enveloped virions like HIV consist of nucleic acid and capsid proteins surrounded by a phospholipid bilayer envelope and its associated proteins. Glycoproteins embedded in the viral envelope are used to attach to host cells. Other envelope proteins include the matrix proteins that stabilize the envelope and often play a role in the assembly of progeny virions. Chicken pox, influenza, and mumps are examples of diseases caused by viruses with envelopes. Because of the fragility of the envelope, non-enveloped viruses are more resistant to changes in temperature, pH, and some disinfectants than are enveloped viruses.

Types of Nucleic Acid

Unlike nearly all living organisms that use DNA as their genetic material, viruses may use either DNA or RNA. The virus core contains the genome or total genetic content of the virus. Viral genomes tend to be small, containing only those genes that encode proteins that the virus cannot obtain from the host cell. This genetic material may be single- or double-stranded. It may also be linear or circular. While most viruses contain a single nucleic acid, others have genomes that have several, called segments.

In DNA viruses, the viral DNA directs the host cell's replication proteins to synthesize new copies of the viral genome and to transcribe and translate that genome into viral proteins. DNA viruses cause human diseases, such as chickenpox, hepatitis B, and some venereal diseases, like herpes and genital warts.

RNA viruses contain only RNA as their genetic material. To replicate their genomes in the host cell, the RNA viruses encode enzymes that can replicate RNA into DNA, which cannot be done by the host cell. These RNA polymerase enzymes are more likely to make copying errors than DNA polymerases and, therefore, often make mistakes during transcription. For this reason, mutations in RNA viruses occur more frequently than in DNA viruses. This causes them to change and adapt more rapidly to their host. Human diseases caused by RNA viruses include hepatitis C, measles, and rabies.

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9.2B: General Morphology

Viruses have a variety of shapes and structures.

Learning Objectives

- Distinguish between the 5 main morphological virus types

Key Points

- Viruses are very small and to reliably visualize them, stains and electron microscopy are needed.
- Each virus is a nucleic acid (RNA or DNA) surrounded by a coating, referred to as an envelope or capsid.
- Viruses encode capsid proteins which encase the nucleic acid. Sometimes, viral proteins combine with host proteins to make the envelope.
- The shape of a viral coat has implications on how a virus infects a host.

Key Terms

- **capsomere**: Any of the individual protein subunits of a viral capsid
- **capsid**: The outer protein shell of a virus.
- **icosahedral**: of, relating to, or having the shape of an icosahedron

Viruses display a wide diversity of shapes and sizes, called morphologies. In general, there are five main morphological virus types:

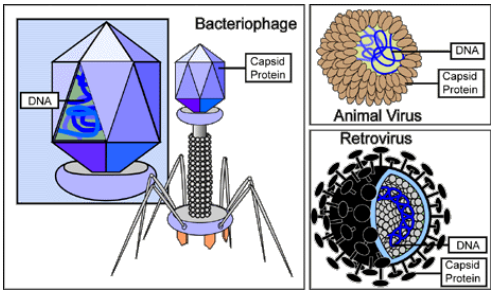

Figure: **Viral structure**: An outline of the structures of some common viral types.

1. Helical – These viruses are composed of a single type of capsomer stacked around a central axis to form a helical structure, which may have a central cavity, or hollow tube.
2. Icosahedral – Most animal viruses are icosahedral or near-spherical with icosahedral symmetry.
3. Prolate – This is an isosahedron elongated along one axis and is a common arrangement of the heads of bacteriophages.
4. Envelope – Some species of virus envelop themselves in a modified form of one of the cell membranes, either the outer membrane surrounding an infected host cell or internal membranes such as nuclear membrane or endoplasmic reticulum, thus gaining an outer lipid bilayer known as a viral envelope.
5. Complex – These viruses possess a capsid that is neither purely helical nor purely icosahedral, and that may possess extra structures such as protein tails or a complex outer wall.

A complete virus particle, known as a virion, consists of nucleic acid surrounded by a protective coat of protein called a capsid. These are formed from identical protein subunits called capsomeres. Viruses can have a lipid “envelope” derived from the host cell membrane. The capsid is made from proteins encoded by the viral genome and its shape serves as the basis for morphological distinction. Virally coded protein subunits will self-assemble to form a capsid, in general requiring the presence of the virus genome. Complex viruses code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The capsid and entire virus structure can be mechanically (physically) probed through atomic force microscopy.

viruses are much smaller than bacteria. Most viruses that have been studied have a diameter between 20 and 300 nanometers. Some filoviruses have a total length of up to 1400 nm; their diameters are only about 80 nm. Most viruses, such as virions, cannot be seen with an optical microscope, so scanning and transmission electron microscopes are used to visualize them.

To increase the contrast between viruses and the background, electron-dense “stains” are used. These are solutions of salts of heavy metals, such as tungsten, that scatter the electrons from regions covered with the stain. When virions are coated with stain (positive staining), fine detail is obscured. Negative staining overcomes this problem by staining the background only.

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9.2C: Complex and Asymmetrical Virus Particles

Complex viruses are often asymetrical or symetrical in combination with other structures such as a tail.

Learning Objectives

- Break down the differences between complex and asymmetrical viruses

Key Points

- Viruses can be structurally very different.
- Some complex viruses are large enough to be visible with a light microscope.
- The viruses of archaea are unique compared to other viruses.

Key Terms

- **capsid**: The outer protein shell of a virus.
- **poxvirus**: Any of the group of DNA viruses belonging to the family Poxviridae, which cause pox diseases in vertebrates.

Viruses have many structural shapes, often falling into certain categories. While some have symmetrical shapes, viruses with asymmetrical structures are referred to as “complex. ” These viruses possess a capsid that is neither purely helical nor purely icosahedral, and may possess extra structures such as protein tails or a complex outer walls.

Some bacteriophages, such as Enterobacteria phage T4, have a complex structure consisting of an icosahedral head bound to a helical tail, which may have a hexagonal base plate with protruding protein tail fibers. This tail structure acts like a molecular syringe, attaching to the bacterial host and then injecting the viral genome into the cell.

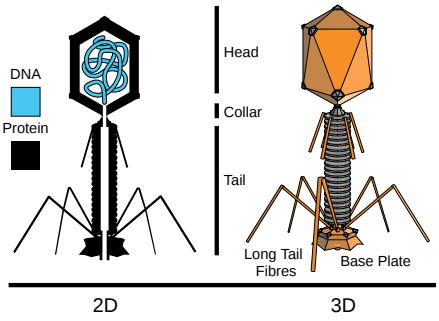

Figure: **T4 Bacteriophage**: T4 is a bacteriophage that infects E. coli and is referred to as a complex virus. Although it has an icosahedral head, its tail makes it asymmetrical, or complex in terms of structure.

The poxviruses are large, complex viruses that have an unusual morphology. The viral genome is associated with proteins within a central disk structure known as a nucleoid. The nucleoid is surrounded by a membrane and two lateral bodies of unknown function. The virus has an outer envelope with a thick layer of protein studded over its surface. The whole virion is slightly pleiomorphic, ranging from ovoid to brick shape.

Mimivirus is the largest characterized virus, with a capsid diameter of 400 nm. Protein filaments measuring 100 nm project from the surface. The capsid appears hexagonal under an electron microscope, therefore the capsid is probably icosahedral. In 2011, researchers discovered a larger virus on the ocean floor off the coast of Las Cruces, Chile. Provisionally named *Megavirus chilensis*, it can be seen with a basic optical microscope.

Some viruses that infect archaea have complex structures unrelated to any other form of virus. These include a wide variety of unusual shapes, ranging from spindle-shaped structures, to viruses that resemble hooked rods, teardrops, or even bottles. Other archaeal viruses resemble the tailed bacteriophages, and can have multiple tail structures.

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SECTION OVERVIEW

9.3: Classifying Viruses

Topic hierarchy

9.3A: The International Committee on Taxonomy of Viruses

9.3B: The Baltimore Virus Classification

9.3C: Evolution of Viruses

9.3D: Medical Importance of Viruses

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9.3A: The International Committee on Taxonomy of Viruses

The International Committee on Taxonomy of Viruses (ICTV) establishes guidelines to maintain viral family uniformity.

Learning Objectives

- Describe the purpose and objectives of the International Committee on Taxonomy of Viruses

Key Points

- Only a small part of the total diversity of viruses has been studied. Analyses of samples from humans found that about 20% of the virus sequences recovered have not been seen before.
- A large majority of sequences of viral samples from the environment, such as from seawater and ocean sediments, are completely novel.
- The general taxonomic structure is as follows: Order (-virales); Family (-viridae); Subfamily (-virinae); Genus (-virus); Species (-virus).

Key Terms

- **taxonomy**: the academic discipline of defining groups of biological organisms on the basis of shared characteristics and giving names to those groups. Each group is given a rank and groups of a given rank can be aggregated to form a super group of higher rank and thus create a hierarchical classification.

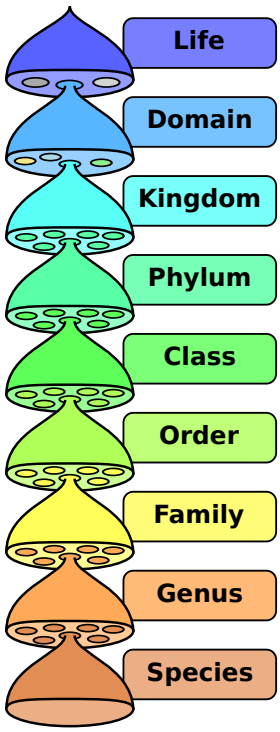

Figure: **Microbial taxonomy**: Taxonomic ranks

The International Committee on Taxonomy of Viruses (ICTV) is a committee which authorizes and organizes the taxonomic classification of viruses. They have developed a universal taxonomic scheme for viruses and aim to describe all the viruses of living organisms. Members of the committee are considered to be world experts on viruses. The committee formed from and is governed by the Virology Division of the International Union of Microbiological Societies. Detailed work such as delimiting the boundaries of species within a family is typically done by study groups, which consist of experts in the families. The committee also operates an authoritative database (ICTVdB) containing taxonomic information for 1,950 virus species, as of 2005. It is open to the public and is searchable by several different means.

The official objectives of the ICTV are:

1. To develop an internationally agreed upon taxonomy for viruses.

2. To develop internationally agreed upon names for virus taxa, including species and subviral agents.
3. To communicate taxonomic decisions to all users of virus names, in particular the international community of virologists, by publications and via the Internet.
4. To maintain an index of virus names.
5. To maintain an ICTV database on the Internet, that records the data that characterize each named viral taxon, together with the common names of each taxon in all major languages.

Proposals for new names, name changes, and the establishment and taxonomic placement of taxa are handled by the Executive Committee of the ICTV in the form of proposals. All relevant ICTV subcommittees and study groups are consulted prior to a decision being made. The name of a taxon has no status until it has been approved by ICTV, and names will only be accepted if they are linked to approved hierarchical taxa. If no suitable name is proposed for a taxon, the taxon may be approved and the name be left undecided until the adoption of an acceptable international name, when one is proposed to and accepted by ICTV. Names must not convey a meaning for the taxon which would seem to either exclude viruses which are rightfully members of that taxa, exclude members which might one day belong to that taxa, or include viruses which are members of different taxa.

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9.3B: The Baltimore Virus Classification

The Baltimore classification groups viruses into families depending on their type of genome.

Learning Objectives

- List the characteristics of viruses that are useful for Baltimore classification

Key Points

- Viral genome ‘s nucleic acid (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication determine its class.
- Other classifications are determined by the disease caused by the virus or its morphology.
- Viruses can be placed in one of the seven groups.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

Virus classification is the process of naming viruses and placing them into a taxonomic system. Much like the classification systems used for cellular organisms, virus classification is the subject of ongoing debate and proposals. This is mainly due to the pseudo-living nature of viruses, which is to say they are non-living particles with some chemical characteristics similar to those of life. As such, they do not fit neatly into the established biological classification system in place for cellular organisms.

Baltimore classification (first defined in 1971) is a classification system that places viruses into one of seven groups depending on a combination of their nucleic acid (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication. Named after David Baltimore, a Nobel Prize-winning biologist, these groups are designated by Roman numerals and discriminate viruses depending on their mode of replication and genome type. Other classifications are determined by the disease caused by the virus or its morphology, neither of which are satisfactory due to different viruses either causing the same disease or looking very similar. In addition, viral structures are often difficult to determine under the microscope.

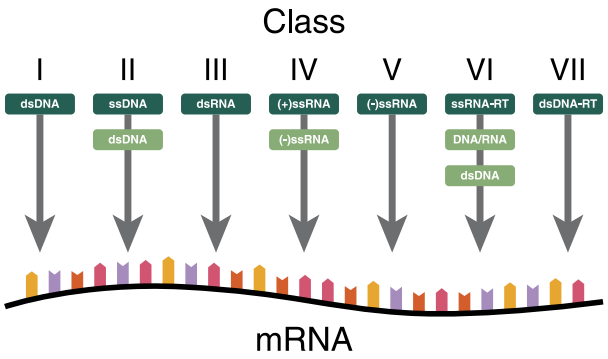

Figure: **Viral classes**: Baltimore classification of viruses

Classifying viruses according to their genome means that those in a given category will all behave in a similar fashion, offering some indication of how to proceed with further research. Viruses can be placed in one of the seven following groups:

1. I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)
2. II: ssDNA viruses (+)sense DNA (e.g. Parvoviruses)
3. III: dsRNA viruses (e.g. Reoviruses)
4. IV: (+)ssRNA viruses (+)sense RNA (e.g. Picornaviruses, Togaviruses)
5. V: (−)ssRNA viruses (−)sense RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
6. VI: ssRNA-RT viruses (+)sense RNA with DNA intermediate in life-cycle (e.g. Retroviruses)
7. VII: dsDNA-RT viruses (e.g. Hepadnaviruses)

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9.3C: Evolution of Viruses

The evolution of viruses is speculative as they do not fossilize; biochemical and genetic information is used to create virus histories.

Learning Objectives

- Describe the difficulties in determining the origin of viruses

Key Points

- Scientists agree that viruses don't have a single common ancestor, but have yet to agree on a single hypothesis about virus origins.
- The devolution or the regressive hypothesis suggests that viruses evolved from free-living cells.
- The escapist or the progressive hypothesis suggests that viruses originated from RNA and DNA molecules that escaped from a host cell.
- The self-replicating hypothesis posits a system of self-replication that most probably involves evolution alongside the host cells.

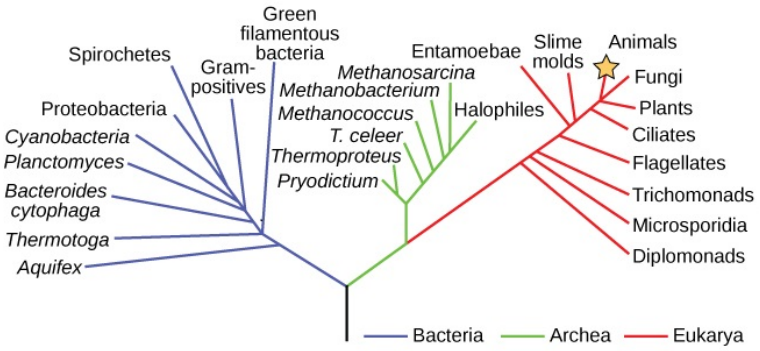
Key Terms

- **self-replicating**: able to generate a copy of itself
- **devolution**: degeneration (as opposed to evolution)

Evolution of Viruses

Although biologists have accumulated a significant amount of knowledge about how present-day viruses evolve, much less is known about how viruses originated in the first place. When exploring the evolutionary history of most organisms, scientists can look at fossil records and similar historic evidence. However, viruses do not fossilize, so researchers must conjecture by investigating how today's viruses evolve and by using biochemical and genetic information to create speculative virus histories.

While most findings agree that viruses don't have a single common ancestor, scholars have yet to find one hypothesis about virus origins that is fully accepted in the field. One possible hypothesis, called devolution or the regressive hypothesis, proposes to explain the origin of viruses by suggesting that viruses evolved from free-living cells. However, many components of how this process might have occurred are a mystery. A second hypothesis (called escapist or the progressive hypothesis) accounts for viruses having either an RNA or a DNA genome and suggests that viruses originated from RNA and DNA molecules that escaped from a host cell. A third hypothesis posits a system of self-replication similar to that of other self-replicating molecules, probably evolving alongside the cells they rely on as hosts; studies of some plant pathogens support this hypothesis.



(a) Rooted phylogenetic tree

Figure: **Common ancestor tree of life**: This phylogenetic tree of the three domains of life (Bacteria, Archaea, and Eukarya) attempts to identify when various species diverged from a common ancestor. Finding a common ancestor for viruses has proven to be far more difficult, especially since they do not fossilize.

As technology advances, scientists may develop and refine further hypotheses to explain the origin of viruses. The emerging field called virus molecular systematics attempts to do just that through comparisons of sequenced genetic material. These researchers hope to one day better understand the origin of viruses, a discovery that could lead to advances in the treatments for the ailments they produce.

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9.3D: Medical Importance of Viruses

Viruses are obligate intracellular parasites that hijack a host cell's machinery to replicate, thereby causing disease.

Learning Objectives

- Describe the fundamental characteristics of viruses

Key Points

- Viruses multiply by taking control of the host cell's genetic material and regulating the synthesis and assembly of new viruses.
- Viruses are able to infect a host cell and cause acute diseases or alter its genetic material to cause chronic diseases such as cancer.
- Most viral infections can resolve in weeks but others are the cause of more serious, debilitating and sometimes fatal diseases.

Key Terms

- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.
- **eradication**: the act of plucking up by the roots; a rooting out; extirpation; utter destruction.

Viruses are extremely diverse and have evolved to infect nearly all life forms. Amid this diversity, viruses with similar genome organizations exhibit major conserved themes in their replication strategies. Once inside a cell, all viruses must uncoat, replicate, and transcribe their genomes, and then repackage their genomes into viral progeny that are released from cells. RNA viruses in particular must coordinate the switch between plus and minus strand synthesis and between replication and transcription while protecting their genomes from cellular nucleases. Because of the conserved nature of a virus 's intracellular life cycle, fundamental advances in our understanding of replication have come from viruses that infect both animal and non-animal hosts.

The devastating effects of viral diseases such as AIDs, smallpox, polio, influenza, diarrhea, and hepatitis are well known, and studies of viral pathogens are easily justified from a world health perspective. Sobering examples of emerging viral diseases have occurred. Among these are the sudden emergence of the coronavirus that causes severe acute respiratory syndrome (SARS), the continued transmission of an avian influenza virus to humans ("bird flu"), and the isolation of poliovirus vaccine -wild type recombinants that have hampered poliovirus eradication efforts. In addition, the threat of bioterrorism became a reality on U.S. soil, creating an obligation for scientists to respond with aggressive countermeasures. Vaccination remains the preferred strategy for controlling viral diseases because the intimate association of viruses with the host cellular machinery complicates the development of safe drugs. However, certain viruses have proven difficult targets for vaccines, and antiviral drugs provide the only option for controlling disease.

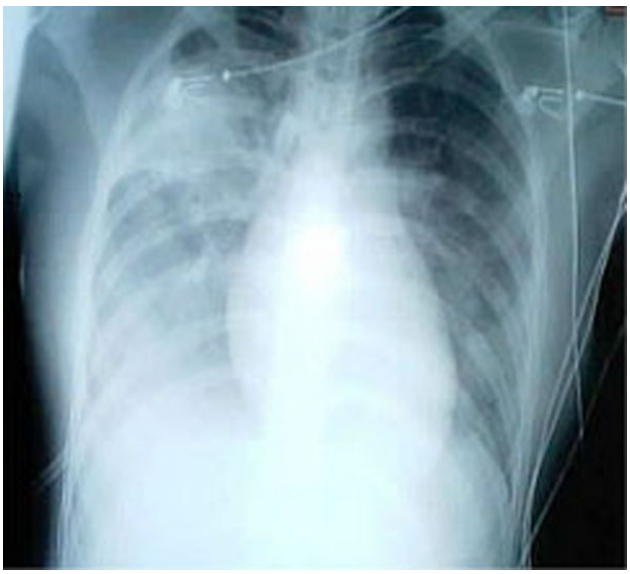

Figure: **Medical importance of SARS**: A chest x-ray showing increased opacity in both lungs, indicative of pneumonia, in a patient with SARS.

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SECTION OVERVIEW

9.4: Culturing Viruses

Topic hierarchy

9.4A: Batch Culture of Bacteriophages

9.4B: Tissue Culture of Animal Viruses

9.4C: Inoculation of Live Animals

9.4D: Viral Identification

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9.4A: Batch Culture of Bacteriophages

Bacteriophage cultures require host cells in which the virus or phage multiply.

Learning Objectives

- Define the reasons for, and ways to batch culture bacteriophages

Key Points

- A bacteriophage is a type of virus that infects bacteria. It does so by injecting genetic material – either DNA or RNA – which it carries enclosed in an outer protein capsid.
- To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella.
- Phage virions do not move independently, they must rely on random encounters with the right receptors when in solution (blood, lymphatic circulation, irrigation, soil water, etc.).

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.

Strategies of Replication

Virus or phage cultures require host cells in which to multiply. For bacteriophages, cultures are grown by infecting bacterial cells. The phage can then be isolated from the resulting plaques in a lawn of bacteria on a plate.

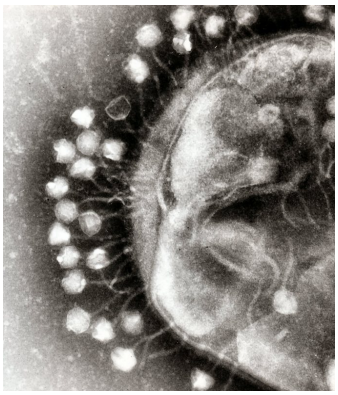

Figure: **Bacteriophages infecting a bacteria**: Virus or phage cultures require host cells in which to multiply. For bacteriophages, cultures are grown by infecting bacterial cells. The phage can then be isolated from the resulting plaques in a lawn of bacteria on a plate.

A bacteriophage is any one of a number of viruses that infect bacteria. They do this by injecting genetic material, which they carry enclosed in an outer protein capsid, into a host bacterial cell. The genetic material can be ssRNA, dsRNA, ssDNA, or dsDNA (‘ss-‘ or ‘ds-‘ prefix denotes single-strand or double-strand), along with either circular or linear arrangements.

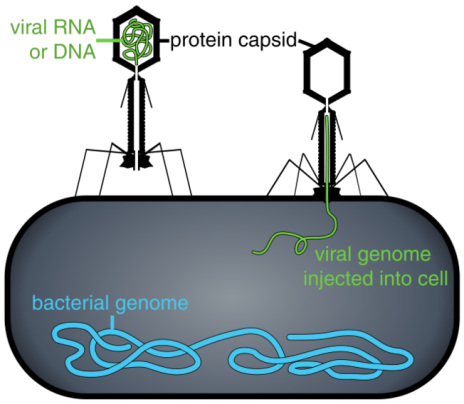

Figure: **Bacteriophage**: Diagram of how some bacteriophages infect bacterial cells.

To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella. This specificity means a bacteriophage can infect only those bacteria bearing receptors to which they can bind, which in turn determines the phage's host range. Host growth conditions also influence the ability of the phage to attach and invade them. As phage virions do not move independently, they must rely on random encounters with the right receptors when in solution within blood, lymphatic circulation, irrigation, soil water, or other environments..

Phages may be released via cell lysis, by extrusion, or, in a few cases, by budding. Lysis, by tailed phages, is achieved by an enzyme called endolysin, which attacks and breaks down the cell wall peptidoglycan. An altogether different phage type, the filamentous phages, make the host cell continually secrete new virus particles. Released virions are described as free, and, unless defective, are capable of infecting a new bacterium. Budding is associated with certain Mycoplasma phages. In contrast to virion release, phages displaying a lysogenic cycle do not kill the host but, rather, become long-term residents as prophage.

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9.4B: Tissue Culture of Animal Viruses

Viruses cannot be grown in standard microbiological broths or on agar plates, instead they have be to cultured inside suitable host cells.

Learning Objectives

- Discover the use of, and reasons for, culturing animal viruses in host cells

Key Points

- Tissue culture is a useful method for cultivating clinical samples suspected of harboring a virus. This method helps with the detection, identification, and characterization of viruses in the laboratory.
- Tissue culture of animal viruses involves growing animal cells in flasks using various broth media and then infecting these cells with virus.
- Transfection can be carried out using calcium phosphate, by electroporation, or by mixing a cationic lipid with the material to produce liposomes, which fuse with the cell membrane and deposit their cargo inside.
- Cytopathic effect is a non-lytic damage that viruses cause to cells. These vary in their manifestation and damaging effect.

Key Terms

- **cell culture**: The complex process by which cells are grown under controlled conditions, generally outside of their natural environment.
- **cytopathic effect**: Refers to degenerative changes in cells, especially in tissue culture, and may be associated with the multiplication of certain viruses.

Cell culture is the complex process by which cells are grown under controlled conditions, generally outside of their natural environment. In practice, the term “cell culture” now refers to the culturing of cells derived from multi-cellular eukaryotes, especially animal cells. However, there are also cultures of plants, fungi, and microbes, including viruses, bacteria, and protists. The historical development and methods of cell culture are closely interrelated to those of tissue culture and organ culture. Animal cell culture became a common laboratory technique in the mid-1900’s, but the concept of maintaining live cell lines separated from their original tissue source was discovered in the 19th century.

Viruses are obligate intracellular parasites that require living cells in order to replicate. Cultured cells, eggs, and laboratory animals may be used for virus isolation. Although embroyonated eggs and laboratory animals are very useful for the isolation of certain viruses, cell cultures are the sole system for virus isolation in most laboratories. The development of methods for cultivating animal cells has been essential to the progress of animal virology. To prepare cell cultures, tissue fragments are first dissociated, usually with the aid of trypsin or collagenase. The cell suspension is then placed in a flat-bottomed glass or plastic container (petri dish, a flask, a bottle, test tube) together with a suitable liquid medium. e.g. Eagle’s, and an animal serum. After a variable lag, the cells will attach and spread on the bottom of the container and then start dividing, giving rise to a primary culture. Attachment to a solid support is essential for the growth of normal cells.

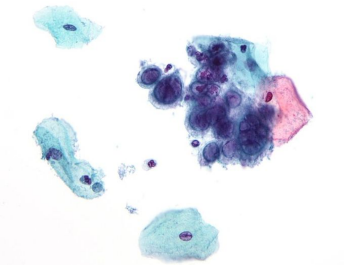

Figure: **Cytopathic effect**: Viral cytopathic effect of herpes simplex virus.

Cell cultures vary greatly in their susceptibility to different viruses. It is of utmost importance that the most sensitive cell cultures are used for a particular suspected virus. Specimens for cell culture should be transported to the laboratory as soon as possible upon being taken. Swabs should be put in a vial containing virus transport medium. Bodily fluids and tissues should be placed in a sterile container. Upon receipt, the specimen is inoculated into several different types of cell culture depending on the nature of the specimen and the clinical presentation. The maintenance media should be changed after one hour or the next morning. The

inoculated tubes should be incubated at 35-37°C in a rotating drum. Rotation is optimal for the isolation of respiratory viruses and result in an earlier appearance of the cytopathic effects (CPE) for many viruses. If stationary tubes are used, it is critical that the culture tubes be positioned so that the cell monolayer is bathed in nutrient medium.

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9.4C: Inoculation of Live Animals

Live animal inoculation is a method used to cultivate viruses.

Learning Objectives

- Describe live animal innoculation

Key Points

- Live inoculation was first used on human volunteers for the study of yellow fever virus.
- Animals of choice for cultivating viruses include monkeys, rabbits, guinea pigs, rats, hamsters, and mice.
- Live animal inoculation requires an experienced personnel to perform various inoculation techniques.

Key Terms

- **latent**: Existing or present but concealed or inactive.
- **oncogenesis**: The formation and development of tumors
- **inoculation**: The introduction of an antigenic substance or vaccine into the body to produce immunity to a specific disease.

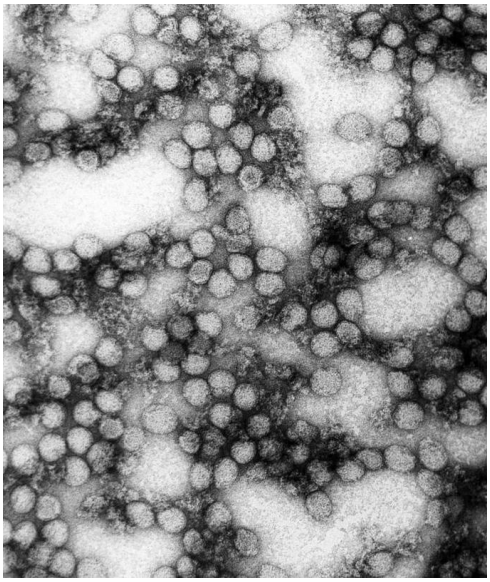

Figure: **Yellow fever virus**: A micrograph of the yellow fever virus.

Viruses are obligate intracellular parasites and cannot grow on inanimate media. They need living cells for replication, which can be provided by inoculation in live animals among other methods used to culture viruses (cell culture or inoculation of embryonated eggs). Inoculation of human volunteers was the only known method of cultivation of viruses and understanding viral disease. In 1900, Reed and his colleagues used human volunteers for their work on yellow fever. Due to serious risk involved, human volunteers are recruited only when no other method is available and the virus is relatively harmless. Smallpox was likely the first disease people tried to prevent by purposely inoculating themselves with other infections and was the first disease for which a vaccine was produced. Today, studying viruses via the inoculation of humans would require a stringent study of ethical practices by an institutional review board.

In the past few decades, animal inoculation has been employed for virus isolation. The laboratory animals used include monkeys, rabbits, guinea pigs, rats, hamsters, and mice. The choice of animals and route of inoculation (intracerebral, intraperitoneal, subcutaneous, intradermal, or intraocular) depends largely on the type of virus to be isolated. Handling of animals and inoculation into various routes requires special experience and training. In addition to virus isolation, animal inoculation can also be used to observe pathogenesis, immune response, epidemiology, and oncogenesis. Growth of the virus in inoculated animals may be indicated by visible lesions, disease, or death. Sometimes, serial passage into animals may be required to obtain visible evidence of viral growth. Animal inoculation has several disadvantages as immunity may interfere with viral growth, and the animal may harbor latent viruses.

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9.4D: Viral Identification

The genetic material within virus particles varies considerably between different types of viruses.

Learning Objectives

- Compare the replication of DNA, RNA, and reverse transcribing viruses

Key Points

- The genome replication of most DNA viruses takes place in the cell's nucleus.
- RNA viruses can be placed into four different groups depending on their modes of replication.
- Reverse transcribing viruses have ssRNA (Retroviridae, Metaviridae, Pseudoviridae) or dsDNA (Caulimoviridae, and Hepadnaviridae) in their particles.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

Replication of Viruses

The genetic material within virus particles and the method by which the material is replicated vary considerably between different types of viruses.

TYPES

DNA viruses: The genome replication of most DNA viruses takes place in the cell's nucleus. If the cell has the appropriate receptor on its surface, these viruses sometimes enter the cell by direct fusion with the cell membrane (e.g., herpesviruses) or, more usually, by receptor-mediated endocytosis. Most DNA viruses are entirely dependent on the host cell's DNA and RNA synthesizing machinery and RNA processing machinery; however, viruses with larger genomes may encode much of this machinery themselves. In eukaryotes the viral genome must cross the cell's nuclear membrane to access this machinery, while in bacteria it need only enter the cell.

RNA viruses: Replication usually takes place in the cytoplasm. RNA viruses can be placed into four different groups, depending on their modes of replication. The polarity of single-stranded RNA viruses largely determines the replicative mechanism, depending on whether or not it can be used directly by ribosomes to make proteins. The other major criterion is whether the genetic material is single-stranded or double-stranded. All RNA viruses use their own RNA replicase enzymes to create copies of their genomes.

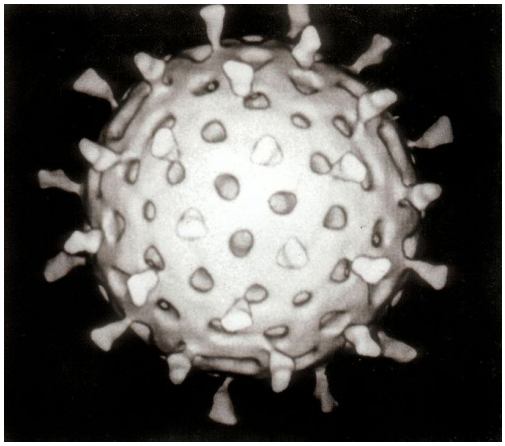

Figure: **Computer assisted reconstruction of a rotavirus particle**: An example of Baltimore Virus classification I: dsDNA virusesII: ssDNA virusesIII: dsRNA virusesIV: (+)ssRNA virusesV: (−)ssRNA virusesVI: ssRNA-RT virusesVII: dsDNA-RT viruses

Reverse transcribing viruses: These have ssRNA (Retroviridae, Metaviridae, Pseudoviridae) or dsDNA (Caulimoviridae, and Hepadnaviridae) in their particles. Reverse transcribing viruses with RNA genomes (retroviruses), use a DNA intermediate to replicate, whereas those with DNA genomes (pararetroviruses) use an RNA intermediate during genome replication. Both types use

a reverse transcriptase, or RNA-dependent DNA polymerase enzyme, to carry out the nucleic acid conversion. Retroviruses integrate the DNA produced by reverse transcription into the host genome as a provirus as a part of the replication process. Pararetroviruses do not, although integrated genome copies, usually of plant pararetroviruses, can give rise to infectious virus. They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine and lamivudine. An example of the first type is HIV, which is a retrovirus. Examples of the second type are the Hepadnaviridae, which includes Hepatitis B virus.

The *Baltimore classification* developed by David Baltimore is a virus classification system that groups viruses into families, depending on their type of genome (DNA, RNA, single-stranded (ss), double-stranded (ds), etc.) and their method of replication. Classifying viruses according to their genome means that those in a given category will all behave in much the same way, which offers some indication of how to proceed with further research.

In summary:

- I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)
- II: ssDNA viruses (+)sense DNA (e.g. Parvoviruses)
- III: dsRNA viruses (e.g. Reoviruses)IV: (+)ssRNA viruses (+)sense RNA (e.g. Picornaviruses, Togaviruses)V: (−)ssRNA viruses (−)sense RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
- VI: ssRNA-RT viruses (+)sense RNA with DNA intermediate in life-cycle (e.g. Retroviruses)
- VII: dsDNA-RT viruses (e.g. Hepadnaviruses)

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SECTION OVERVIEW

9.5: Viral Replication

Topic hierarchy

9.5A: General Features of Virus Replication

9.5B: Steps of Virus Infections

9.5C: Tissue Tropism in Animal Viruses

9.5D: Animal Viruses

9.5E: Plant Virus Life Cycles

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9.5A: General Features of Virus Replication

Virologists describe the formation of viruses during the infection process in target host cells as viral replication.

Learning Objectives

- Outline the features of viral replication

Key Points

- Viral populations do not grow through cell division, because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell.
- The life cycle of viruses differs greatly between species but there are six basic stages in the life cycle of viruses: attachment, penetration (viral entry), uncoating, replication, and lysis.
- Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host's chromosome.

Key Terms

- **lysis**: The disintegration or destruction of cells
- **leukocyte**: A white blood cell.
- **uncoating**: A process in which the viral capsid of a virus is removed, leading to the release of the viral genomic nucleic acid.
- **attachment**: specific binding between viral capsid proteins and specific receptors on the host cellular surface

Multiplication Within the Host Cell

Viral replication is the term used indicate the formation of biological viruses during the infection process in the target host cells. Viruses must first penetrate and enter the cell before viral replication can occur. From the perspective of the virus, the purpose of viral replication is to allow reproduction and survival of its kind. By generating abundant copies of its genome and packaging these copies into viruses, the virus is able to continue infecting new hosts.

Replication between viruses is varied and depends on the type of genes involved. Most DNA viruses assemble in the nucleus; most RNA viruses develop solely in cytoplasm. Viral populations do not grow through cell division, because they are acellular. Instead, they hijack the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble inside the cell.

The life cycle of viruses differs greatly between species but there are six common basic stages:

Attachment is a specific binding between viral capsid proteins and specific receptors on the host cellular surface. This specificity determines the host range of a virus. For example, HIV can infect only a limited range of human leukocytes. Its surface protein, gp120, specifically interacts only with the CD4 molecule – a chemokine receptor – which is most commonly found on the surface of CD4+ T-Cells. This mechanism has evolved to favor those viruses that infect only cells within which they are capable of replication. Attachment to the receptor can fore the viral envelope protein to undergo either changes that result in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.

Penetration follows attachment. Virions enter the host cell through receptor-mediated endocytosis or membrane fusion. This is often called *viral entry*. The infection of plant and fungal cells is different from that of animal cells. Plants have a rigid cell wall made of cellulose, and fungi one of chitin, so most viruses can get inside these cells only after trauma to the cell wall. However, nearly all plant viruses (such as tobacco mosaic virus) can also move directly from cell to cell, in the form of single-stranded nucleoprotein complexes, through pores called plasmodesmata. Bacteria, like plants, have strong cell walls that a virus must breach to infect the cell. However, since bacterial cell walls are much less thick than plant cell walls due to their much smaller size, some viruses have evolved mechanisms that inject their genome into the bacterial cell across the cell wall, while the viral capsid remains outside.

Uncoating is a process in which the viral capsid is removed: This may be by degradation by viral or host enzymes or by simple dissociation. In either case the end-result is the release of the viral genomic nucleic acid.

Replication of viruses depends on the multiplication of the genome. This is accomplished through synthesis of viral messenger RNA (mRNA) from "early" genes (with exceptions for positive sense RNA viruses), viral protein synthesis, possible assembly of

viral proteins, then viral genome replication mediated by early or regulatory protein expression. This may be followed, for complex viruses with larger genomes, by one or more further rounds of mRNA synthesis: “late” gene expression is, in general, of structural or virion proteins.

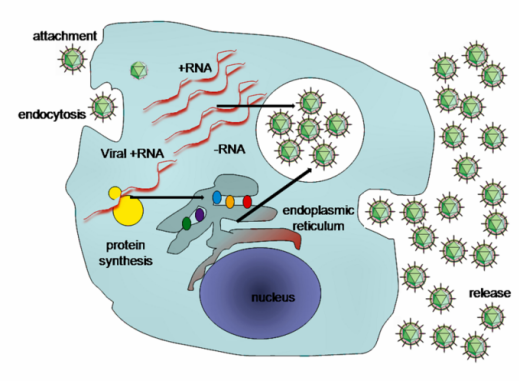

Figure: **Hepatitis C virus**: A simplified diagram of the Hepatitis C virus replication cycle.

Following the structure-mediated self-assembly of the virus particles, some modification of the proteins often occurs. In viruses such as HIV, this modification (sometimes called maturation) occurs after the virus has been released from the host cell.

Viruses can be released from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present. This is a feature of many bacterial and some animal viruses. Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host’s chromosome. The viral genome is then known as a *provirus* or, in the case of bacteriophages a *prophage*. Whenever the host divides, the viral genome is also replicated. The viral genome is mostly silent within the host; however, at some point the provirus or prophage may give rise to active virus, which may lyse the host cells. Enveloped viruses (e.g., HIV) typically are released from the host cell by budding. During this process the virus acquires its envelope, which is a modified piece of the host’s plasma or other internal membrane. The genetic material within virus particles, and the method by which the material is replicated, varies considerably between different types of viruses.

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9.5B: Steps of Virus Infections

Viral infection involves the incorporation of viral DNA into a host cell, replication of that material, and the release of the new viruses.

Learning Objectives

- List the steps of viral replication and explain what occurs at each step

Key Points

- Viral replication involves six steps: attachment, penetration, uncoating, replication, assembly, and release.
- During attachment and penetration, the virus attaches itself to a host cell and injects its genetic material into it.
- During uncoating, replication, and assembly, the viral DNA or RNA incorporates itself into the host cell's genetic material and induces it to replicate the viral genome.
- During release, the newly-created viruses are released from the host cell, either by causing the cell to break apart, waiting for the cell to die, or by budding off through the cell membrane.

Key Terms

- **virion**: a single individual particle of a virus (the viral equivalent of a cell)
- **glycoprotein**: a protein with covalently-bonded carbohydrates
- **retrovirus**: a virus that has a genome consisting of RNA

Steps of Virus Infections

A virus must use cell processes to replicate. The viral replication cycle can produce dramatic biochemical and structural changes in the host cell, which may cause cell damage. These changes, called cytopathic (causing cell damage) effects, can change cell functions or even destroy the cell. Some infected cells, such as those infected by the common cold virus known as rhinovirus, die through lysis (bursting) or apoptosis (programmed cell death or "cell suicide"), releasing all progeny virions at once. The symptoms of viral diseases result from the immune response to the virus, which attempts to control and eliminate the virus from the body and from cell damage caused by the virus. Many animal viruses, such as HIV (Human Immunodeficiency Virus), leave the infected cells of the immune system by a process known as budding, where virions leave the cell individually. During the budding process, the cell does not undergo lysis and is not immediately killed. However, the damage to the cells that the virus infects may make it impossible for the cells to function normally, even though the cells remain alive for a period of time. Most productive viral infections follow similar steps in the virus replication cycle: attachment, penetration, uncoating, replication, assembly, and release.

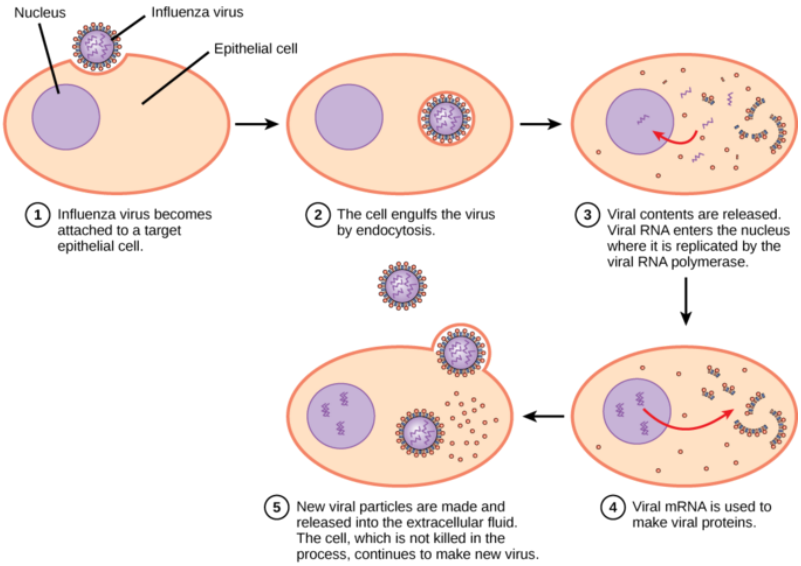

Figure: **Pathway to viral infection**: In influenza virus infection, glycoproteins attach to a host epithelial cell. As a result, the virus is engulfed. RNA and proteins are made and assembled into new virions.

Attachment

A virus attaches to a specific receptor site on the host cell membrane through attachment proteins in the capsid or via glycoproteins embedded in the viral envelope. The specificity of this interaction determines the host (and the cells within the host) that can be infected by a particular virus. This can be illustrated by thinking of several keys and several locks where each key will fit only one specific lock.

Entry

The nucleic acid of bacteriophages enters the host cell naked, leaving the capsid outside the cell. Plant and animal viruses can enter through endocytosis, in which the cell membrane surrounds and engulfs the entire virus. Some enveloped viruses enter the cell when the viral envelope fuses directly with the cell membrane. Once inside the cell, the viral capsid is degraded and the viral nucleic acid is released, which then becomes available for replication and transcription.

Replication and Assembly

The replication mechanism depends on the viral genome. DNA viruses usually use host cell proteins and enzymes to make additional DNA that is transcribed to messenger RNA (mRNA), which is then used to direct protein synthesis. RNA viruses usually use the RNA core as a template for synthesis of viral genomic RNA and mRNA. The viral mRNA directs the host cell to synthesize viral enzymes and capsid proteins, and to assemble new virions. Of course, there are exceptions to this pattern. If a host cell does not provide the enzymes necessary for viral replication, viral genes supply the information to direct synthesis of the missing proteins. Retroviruses, such as HIV, have an RNA genome that must be reverse transcribed into DNA, which then is incorporated into the host cell genome.

To convert RNA into DNA, retroviruses must contain genes that encode the virus-specific enzyme reverse transcriptase, which transcribes an RNA template to DNA. Reverse transcription never occurs in uninfected host cells; the needed enzyme, reverse transcriptase, is only derived from the expression of viral genes within the infected host cells. The fact that HIV produces some of its own enzymes not found in the host has allowed researchers to develop drugs that inhibit these enzymes. These drugs, including the reverse transcriptase inhibitor AZT, inhibit HIV replication by reducing the activity of the enzyme without affecting the host's metabolism. This approach has led to the development of a variety of drugs used to treat HIV and has been effective at reducing the number of infectious virions (copies of viral RNA) in the blood to non-detectable levels in many HIV-infected individuals.

Egress

The last stage of viral replication is the release of the new virions produced in the host organism. They are then able to infect adjacent cells and repeat the replication cycle. As you have learned, some viruses are released when the host cell dies, while other viruses can leave infected cells by budding through the membrane without directly killing the cell.

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9.5C: Tissue Tropism in Animal Viruses

Host tropism refers to the way in which viruses/pathogens determine which cells become infected by a given pathogen.

Learning Objectives

- Explain viral tropism

Key Points

- Viruses must bind to specific cell surface receptors in order to enter a cell.
- If a cell does not express these receptors then the virus cannot normally infect it.
- In virology, Tissue tropism is the cells and tissues of a host which support growth of a particular virus or bacteria. Some viruses have a broad tissue tropism and can infect many types of cells and tissues. Other viruses may infect primarily a single tissue.

Key Terms

- **dendritic cell**: Any cell, having branching processes, that forms part of the mammalian immune system.
- **macrophage**: A white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink. It presents foreign antigens on MHC II to lymphocytes. Part of the innate immune system.

A tropism is a biological phenomenon, indicating growth or turning movement of a biological organism in response to an environmental stimulus. In tropisms, this response is dependent on the direction of the stimulus (as opposed to nastic movements which are non-directional responses). Viruses and other pathogens also affect what is called “host tropism” or “cell tropism. ” Case tropism refers to the way in which different viruses/pathogens have evolved to preferentially target specific host species or specific cell types within those species.

Host tropism is the name given to a process of tropism that determines which cells can become infected by a given pathogen. Host tropism is determined by the biochemical receptor complexes on cell surfaces that are permissive or non-permissive to the docking or attachment of various viruses.

Various factors determine the ability of a pathogen to infect a particular cell. For example, viruses must bind to specific cell surface receptors to enter a cell. If a cell does not express these receptors then the virus cannot normally infect it. Viral tropism is determined by a combination of susceptibility and permissiveness: a host cell must be both permissive (allow viral entry) and susceptible (possess the receptor complement needed for viral entry) for a virus to establish infection. An example of this is the HIV virus, which exhibits tropism for CD4 related immune cells (e.g. T helper cells, macrophages or dendritic cells). These cells express a CD4 receptor, to which the HIV virus can bind, through the gp120 and gp41 proteins on its surface.

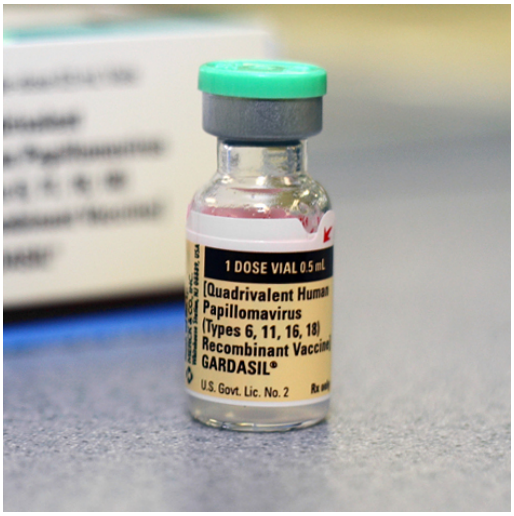

Figure: **Human papillomavirus vaccine**: Gardasil is a human papillomavirus vaccine on the market and it protects against HPV-16 and HPV-18 which cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers.

In virology, Tissue tropism is the cells and tissues of a host that support growth of a particular virus or bacteria. Some viruses have a broad tissue tropism and can infect many types of cells and tissues. Other viruses may infect primarily a single tissue.

Factors influencing viral tissue tropism include: 1) the presence of cellular receptors permitting viral entry, 2) availability of transcription factors involved in viral replication, 3) the molecular nature of the viral tropogen, and 4) the cellular receptors are the proteins found on a cell or viral surface.

These receptors are like keys allowing the viral cell to fuse with a cell or attach itself to a cell. The way that these proteins are acquired is through similar process to that of an infection cycle.

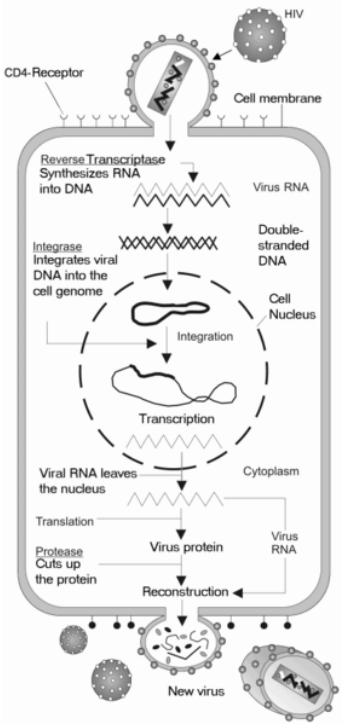

Figure: **HIV life cycle**: HIV has a gp120 which is precisely what the CD4 marker is on the surface of the macrophages and T cells. Therefore, HIV can enter T cells and macrophages.

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9.5D: Animal Viruses

Animal viruses have their genetic material copied by a host cell after which they are released into the environment to cause disease.

Learning Objectives

- Describe various animal viruses and the diseases they cause

Key Points

- Animal viruses may enter a host cell by either receptor -mediated endocytosis or by changing shape and entering the cell through the cell membrane.
- Viruses cause diseases in humans and other animals; they often have to run their course before symptoms disappear.
- Examples of viral animal diseases include hepatitis C, chicken pox, and shingles.

Key Terms

- **receptor-mediated endocytosis**: a process by which cells internalize molecules (endocytosis) by the inward budding of plasma membrane vesicles containing proteins with receptor sites specific to the molecules being internalized

Animal Viruses

Animal viruses, unlike the viruses of plants and bacteria, do not have to penetrate a cell wall to gain access to the host cell. Non-enveloped or “naked” animal viruses may enter cells in two different ways. When a protein in the viral capsid binds to its receptor on the host cell, the virus may be taken inside the cell via a vesicle during the normal cell process of receptor-mediated endocytosis. An alternative method of cell penetration used by non-enveloped viruses is for capsid proteins to undergo shape changes after binding to the receptor, creating channels in the host cell membrane. The viral genome is then “injected” into the host cell through these channels in a manner analogous to that used by many bacteriophages. Enveloped viruses also have two ways of entering cells after binding to their receptors: receptor-mediated endocytosis and fusion. Many enveloped viruses enter the cell by receptor-mediated endocytosis in a fashion similar to some non-enveloped viruses. On the other hand, fusion only occurs with enveloped virions. These viruses, which include HIV among others, use special fusion proteins in their envelopes to cause the envelope to fuse with the plasma membrane of the cell, thus releasing the genome and capsid of the virus into the cell cytoplasm.

After making their proteins and copying their genomes, animal viruses complete the assembly of new virions and exit the cell. Using the example of HIV, enveloped animal viruses may bud from the cell membrane as they assemble themselves, taking a piece of the cell’s plasma membrane in the process. On the other hand, non-enveloped viral progeny, such as rhinoviruses, accumulate in infected cells until there is a signal for lysis or apoptosis, and all virions are released together.

Animal viruses are associated with a variety of human diseases. Some of them follow the classic pattern of acute disease, where symptoms worsen for a short period followed by the elimination of the virus from the body by the immune system with eventual recovery from the infection. Examples of acute viral diseases are the common cold and influenza. Other viruses cause long-term chronic infections, such as the virus causing hepatitis C, whereas others, like herpes simplex virus, cause only intermittent symptoms. Still other viruses, such as human herpes viruses 6 and 7, which in some cases can cause the minor childhood disease roseola, often successfully cause productive infections without causing any symptoms at all in the host; these patients have an asymptomatic infection.

In hepatitis C infections, the virus grows and reproduces in liver cells, causing low levels of liver damage. The damage is so low that infected individuals are often unaware that they are infected, with many infections only detected by routine blood work on patients with risk factors such as intravenous drug use. Since many of the symptoms of viral diseases are caused by immune responses, a lack of symptoms is an indication of a weak immune response to the virus. This allows the virus to escape elimination by the immune system and persist in individuals for years, while continuing to produce low levels of progeny virions in what is known as a chronic viral disease. Chronic infection of the liver by this virus leads to a much greater chance of developing liver cancer, sometimes as much as 30 years after the initial infection.

As mentioned, herpes simplex virus can remain in a state of latency in nervous tissue for months, even years. As the virus “hides” in the tissue and makes few if any viral proteins, there is nothing for the immune response to act against; immunity to the virus slowly declines. Under certain conditions, including various types of physical and psychological stress, the latent herpes simplex virus may be reactivated and undergo a lytic replication cycle in the skin, causing the lesions associated with the disease. Once

virions are produced in the skin and viral proteins are synthesized, the immune response is again stimulated and resolves the skin lesions in a few days by destroying viruses in the skin. As a result of this type of replicative cycle, appearances of cold sores and genital herpes outbreaks only occur intermittently, even though the viruses remain in the nervous tissue for life. Latent infections are common with other herpes viruses as well, including the varicella-zoster virus that causes chickenpox. After having a chickenpox infection in childhood, the varicella-zoster virus can remain latent for many years and reactivate in adults to cause the painful condition known as “shingles”.

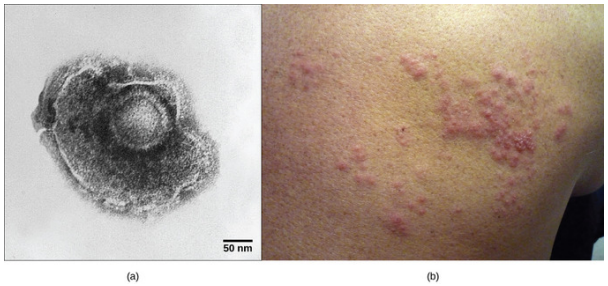

Figure: **Chicken pox virus**: (a) Varicella-zoster, the virus that causes chickenpox, has an enveloped icosahedral capsid visible in this transmission electron micrograph. Its double-stranded DNA genome incorporates into the host DNA and reactivates after latency in the form of (b) shingles, often exhibiting a rash.

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9.5E: Plant Virus Life Cycles

Plant viruses are often spread from plant to plant by organisms known as vectors.

Learning Objectives

- Outline plant virus life cycles

Key Points

- Plant viruses are harmless to humans and other animals because they can only reproduce in living plant cells.
- For the virus to reproduce and thereby establish infection, it must enter cells of the host organism and use those cells' materials.
- A virus must take control of the host cell's replication mechanisms. At this stage a distinction between susceptibility and permissibility of a host cell is made.
- After control is established and the environment is set for the virus to begin making copies of itself, replication occurs quickly by the millions.

Key Terms

- **vector**: A carrier of a disease-causing agent.

Plant viruses are viruses that affect plants. Like all other viruses, plant viruses are obligate intracellular parasites that do not have the molecular machinery to replicate without a host. Plant viruses are pathogenic to higher plants.

There are many types of plant virus, but often they only cause a loss of yield, and it is not economically viable to try to control them. Plant viruses are often spread from plant to plant by organisms (vectors). These are normally insects, but some fungi, nematode worms and single-celled organisms have been shown to be vectors. When control of plant virus infections is considered economical, (for perennial fruits for example), efforts are concentrated on killing the vectors and removing alternate hosts such as weeds. Plant viruses are harmless to humans and other animals because they can only reproduce in living plant cells.

Viral Life Cycle

For the virus to reproduce and thereby establish infection, it must enter cells of the host organism and use those cells' materials. To enter the cells, proteins on the surface of the virus interact with proteins of the cell. Attachment, or adsorption, occurs between the viral particle and the host cell membrane. A hole forms in the cell membrane, then the virus particle or its genetic contents are released into the host cell, where viral reproduction may commence. Next, a virus must take control of the host cell's replication mechanisms. At this stage, a distinction between susceptibility and permissibility of a host cell is made. Permissibility determines the outcome of the infection. After control is established and the environment is set for the virus to begin making copies of itself, replication occurs quickly by the millions. After a virus has made many copies of itself, it usually has exhausted the cell of its resources. The host cell is now no longer useful to the virus, therefore the cell often dies and the newly produced viruses must find a new host. The process by which virus progeny are released to find new hosts, is called shedding. This is the final stage in the viral life cycle. Some viruses can "hide" within a cell, either to evade the host cell defenses or immune system, or simply because it is not in the best interest of the virus to continually replicate. This hiding is deemed latency. During this time, the virus does not produce any progeny, it remains inactive until external stimuli—such as light or stress—prompts it to activate.

Viruses can be spread by direct transfer of sap, and by contact of a wounded plant with a healthy one. Such contact may occur during agricultural practices, when damage is caused by tools or hands, or naturally, when an animal feeds on the plant. Generally Tobacco mosaic virus (TMV), potato viruses, and cucumber mosaic viruses are transmitted via sap.

Tobacco mosaic virus and Cauliflower mosaic virus (CaMV) are frequently used in plant molecular biology. Of special interest is the CaMV 35S promoter, which is a very strong promoter most frequently used in plant transformations.

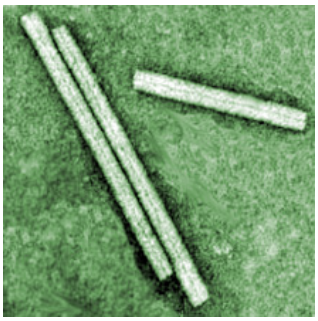

Figure: **Tobacco Mosaic Virus**: Tobacco mosaic virus (TMV) is a positive-sense single stranded RNA virus that infects plants, especially tobacco and other members of the family Solanaceae. The infection causes characteristic patterns (mottling and discoloration) on the leaves (hence the name). TMV was the first virus to be discovered. Although it was known from the late 19th century that an infectious disease was damaging tobacco crops, it was not until 1930 that the infectious agent was determined to be a virus.

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SECTION OVERVIEW

9.6: Subviral Entities

Topic hierarchy

9.6A: Defective Viruses

9.6B: Viroids

9.6C: Prions

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9.6A: Defective Viruses

Learning Objectives

- Distinguish between defective viruses, satellite viruses, and helper viruses

Virologists also study subviral particles, infectious entities notably smaller and simpler than viruses:

- viroids (naked circular RNA molecules infecting plants)
- satellites (nucleic acid molecules with or without a capsid that require a helper virus for infection and reproduction)
- prions (proteins that can exist in a pathological conformation that induces other prion molecules to assume that same conformation)

Not all viruses can reproduce in a host cell by themselves. Since viruses are so small, the size of their genome is limited. For example, some viruses have coded instructions for only making a few different proteins for the viruses' capsid. On the other hand, the human genome codes for over 30,000 different proteins. Therefore, the lack of coded instructions causes some viruses to need the presence of other viruses to help them reproduce themselves. Such viruses are called replication defective.

Satellites depend on co-infection of a host cell with a helper virus for productive multiplication. Their nucleic acids have substantially distinct nucleotide sequences from either their helper virus or host. When a satellite subviral agent encodes the coat protein in which it is encapsulated, it is then called a satellite virus. Satellite viral particles should not be confused with satellite DNA.

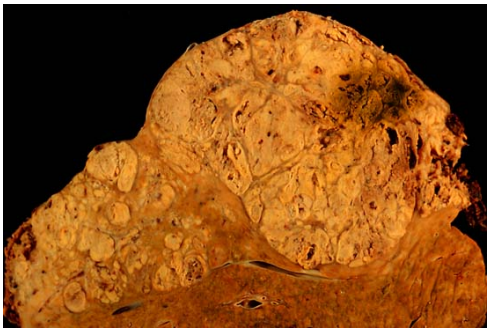

Figure: ***Hepatocellular Carcinoma****: Cirrhosis leading to hepatocellular carcinoma (autopsy specimen). The photo shows a view of a longitudinal slice taken through the full length of the liver.*

The hepatitis delta virus of humans has an RNA genome similar to viroids, but has a protein coat derived from hepatitis B virus and cannot produce one of its own. Therefore, it is a defective virus and cannot replicate without the help of hepatitis B virus. In similar manner, the sputnik virophage is dependent on mimivirus, which infects the protozoan Acanthamoeba castellanii. These viruses that are dependent on the presence of other virus species in the host cell are called satellites. They may represent evolutionary intermediates of viroids and viruses.

Hepatitis D, also referred to as hepatitis D virus (HDV) and classified as Hepatitis delta virus, is a disease caused by a small circular enveloped RNA virus. It is one of five known hepatitis viruses: A, B, C, D, and E. HDV is considered to be a subviral satellite because it can only propagate in the presence of the hepatitis B virus (HBV). Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or superimposed on chronic hepatitis B or hepatitis B carrier state (superinfection). Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections of 20%.

Key Points

- Not all viruses can reproduce in a host cell by themselves. Since viruses are so small, the size of their genome is limited. The lack of coded instructions causes some viruses to need the presence of other viruses to help them reproduce themselves. Such viruses are called replication defective.
- A satellite is a subviral agent composed of nucleic acid that depends on the co- infection of a host cell with a helper or master virus for its multiplication. When a satellite encodes the coat protein in which its nucleic acid is encapsidated it is referred to as

a satellite virus.

- These viruses that are dependent on the presence of other virus species in the host cell are called satellites and may represent evolutionary intermediates of viroids and viruses.

Key Terms

- **Helper virus**: A helper virus is a virus used when producing copies of a helper dependent viral vector which does not have the ability to replicate on its own. The helper virus is used to coinfect cells alongside the viral vector and provides the necessary enzymes for replication of the genome of the viral vector.
- **Satellite**: A subviral agent composed of nucleic acid that depends on the co-infection of a host cell with a helper or master virus for its multiplication.

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9.6B: Viroids

Learning Objectives

- Relate the structure and replication of a viroid to its ability to cause diseases in plants

Viroids are plant pathogens that consist of a short stretch (a few hundred nucleobases) of highly complementary, circular, single-stranded RNA without the protein coat that is typical for viruses. In comparison, the genome of the smallest known viruses capable of causing an infection by themselves is around 2 kilobases in size. The human pathogen Hepatitis D virus is similar to viroids. Viroids are extremely small in size, ranging from 246 to 467 nucleotide (nt) long genome and consisting of fewer than 10,000 atoms. Viroids were discovered and given this name by Theodor Otto Diener, a plant pathologist at the Agricultural Research Service in Maryland, in 1971.

Viroid RNA does not code for any protein. The replication mechanism involves RNA polymerase II, an enzyme normally associated with synthesis of messenger RNA from DNA, which instead catalyzes “rolling circle” synthesis of new RNA using the viroid’s RNA as template. Some viroids are ribozymes, having catalytic properties which allow self-cleavage and ligation of unit-size genomes from larger replication intermediates. The first viroid to be identified was the potato spindle tuber viroid (PSTVd). Some 33 species have been identified.



Figure: ***Putative secondary structure of the potato spindle tuber viroid.****: black – secondary structure of the viroid red – GAAAC sequence common to all viroids yellow – central conservative sequence blue – nucleotide numbers*

There has long been confusion over how viroids are able to induce symptoms in plants without encoding any protein products within their sequences. Evidence now suggests that RNA silencing is involved in the process. First, changes to the viroid genome can dramatically alter its virulence. This reflects the fact that any siRNAs produced would have less complementary base pairing with target messenger RNA. Secondly, siRNAs corresponding to sequences from viroid genomes have been isolated from infected plants. Finally, transgenic expression of the noninfectious hpRNA of potato spindle tuber viroid develops all the corresponding viroid like symptoms. This evidence indicates that when viroids replicate via a double stranded intermediate RNA, they are targeted by a dicer enzyme and cleaved into siRNAs that are then loaded onto the RNA-induced silencing complex. The viroid siRNAs actually contain sequences capable of complementary base pairing with the plant’s own messenger RNAs and induction of degradation or inhibition of translation is what causes the classic viroid symptoms.

Virusoids are circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. The genome of virusoids consists of several hundred nucleotides and only encodes structural proteins. Virusoids are similar to viroids in size, structure, and means of replication. Virusoids, while being studied in virology, are not considered as viruses but as subviral particles. Since they depend on helper viruses, they are classified as satellites.

The Pospiviroidae are a family of viroids, including the first viroid to be discovered, PSTVd. Their secondary structure is key to their biological activity. The classification of this family is based on differences in the conserved central region sequence. Pospiviroidae replication occurs in an asymmetric fashion via host cell RNA polymerase, RNase, and RNA ligase.

The Avsunviroidae are a family of viroids. At present three members are known. They consist of RNA genomes between 246-375 nucleotides in length. They are single stranded covalent circles and have intramolecular base pairing. All members lack a central conserved region. Replication occurs in the chloroplasts of plant cells. Key features of replication include no helper virus required and no proteins are encoded for. Unlike the other family of viroids, Pospiviroidae, Avsunviroidae are thought to replicate via a symmetrical rolling mechanism. It is thought the positive RNA strand acts as a template to form negative strands with the help of an enzyme thought to be RNA polymerase II. The negative RNA strands are then cleaved by ribozyme activity and circularizes. A second rolling circle mechanism forms a positive strand which is also cleaved by ribozyme activity and then ligated to become circular. The site of replication is unknown, but it is thought to be in the chloroplast and in the presence of Mg2+ ions.

Avocado sunblotch viroid (ASBV) is an important disease affecting avocado trees. Infections result in lower yields and poorer quality fruit. ASBV is the smallest known viroid that infects plants and is transmitted by pollen and infected seeds or budwood. Trees infected with the viroid often show no symptoms other than a reduction in yield. However, they are still carriers and can pass the disease onto other plants. Symptoms in more serious infections include depressed longitudinal streaks of yellow in the fruit. The fruit may also become red or white in color. Symptoms in the leaf are uncommon, but include bleached veins and petioles.

Rectangular cracking patterns also occur in the bark of older branches. Infected but symptomless trees have a higher concentration of viroid particles than those showing symptoms. Symptomless trees also represent a greater danger in terms of spread of the viroid.

Key Points

- Viroid RNA does not code for any protein. The replication mechanism involves RNA polymerase II, an enzyme normally associated with synthesis of messenger RNA from DNA, which instead catalyzes “rolling circle” synthesis of new RNA using the viroid’s RNA as template.
- The first viroid to be identified was potato spindle tuber viroid (PSTVd). Some 33 species have been identified.
- There has long been confusion over how viroids are able to induce symptoms in plants without encoding any protein products within their sequences. Evidence now suggests that RNA silencing is involved in the process.
- Virusoids are circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. Since they depend on helper viruses, they are classified as satellites.

Key Terms

- **Virusoid**: Circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. The genome of virusoids consist of several hundred nucleotides and only encodes structural proteins.
- **viroid**: plant pathogens, of the order Viroidales, that consist of just a short section of RNA but without the protein coat typical of viruses

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9.6C: Prions

Learning Objectives

- Compare the protein-only hypothesis of prion diseases with the virion hypothesis, as well as the heterodimer model and the fibril model of prion replication

A prion is an infectious agent composed of protein in a misfolded form. This is the central idea of the Prion Hypothesis, which remains debated. This is in contrast to all other known infectious agents (virus /bacteria/fungus/parasite) which must contain nucleic acids (either DNA, RNA, or both). The word *prion*, coined in 1982 by Stanley B. Prusiner, is derived from the words protein and infection. Prions are responsible for the transmissible spongiform encephalopathies in a variety of mammals, including bovine spongiform encephalopathy (BSE, also known as “mad cow disease”) in cattle and Creutzfeldt–Jakob disease (CJD) in humans. All known prion diseases affect the structure of the brain or other neural tissue, are currently untreatable and universally fatal.

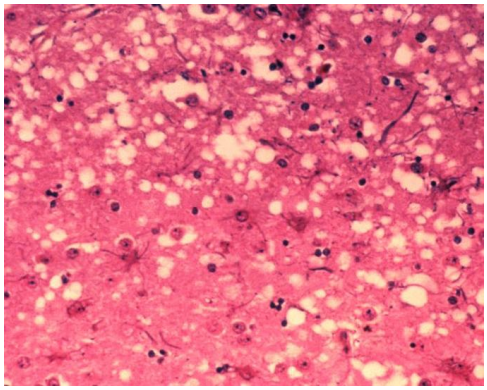

Figure: ***Prion-affected tissue****: This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic “holes” in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.*

Prions propagate by transmitting a misfolded protein state. When a prion enters a healthy organism, it induces existing, properly folded proteins to convert into the disease-associated prion form; it acts as a template to guide the misfolding of more proteins into prion form. These newly-formed prions can then go on to convert more proteins themselves; triggering a chain reaction. All known prions induce the formation of an amyloid fold, in which the protein polymerises into an aggregate consisting of tightly-packed beta sheets. Amyloid aggregates are fibrils, growing at their ends, and replicating when breakage causes two growing ends to become four growing ends.

The incubation period of prion diseases is determined by the exponential growth rate associated with prion replication, which is a balance between the linear growth and the breakage of aggregates. Propagation of the prion depends on the presence of normally-folded protein in which the prion can induce misfolding; animals which do not express the normal form of the prion protein cannot develop nor transmit the disease.

All known mammalian prion diseases are caused by the so-called prion protein, PrP. The endogenous, properly-folded form is denoted PrPC (for Common or Cellular) while the disease-linked, misfolded form is denoted PrPSc (for Scrapie, after one of the diseases first linked to prions and neurodegeneration.) The precise structure of the prion is not known, though they can be formed by combining PrPC, polyadenylic acid, and lipids in a Protein Misfolding Cyclic Amplification (PMCA) reaction.

Proteins showing prion-type behavior are also found in some fungi, which has been useful in helping to understand mammalian prions. Fungal prions do not appear to cause disease in their hosts.

The first hypothesis that tried to explain how prions replicate in a protein-only manner was the heterodimer model. This model assumed that a single PrPSc molecule binds to a single PrPC molecule and catalyzes its conversion into PrPSc. The two PrPSc molecules then come apart and can go on to convert more PrPC. However, a model of prion replication must explain both how prions propagate, and why their spontaneous appearance is so rare. Manfred Eigen showed that the heterodimer model requires PrPSc to be an extraordinarily effective catalyst, increasing the rate of the conversion reaction by a factor of around 10^{15}. This

problem does not arise if PrPSc exists only in aggregated forms such as amyloid, where cooperativity may act as a barrier to spontaneous conversion. What is more, despite considerable effort, infectious monomeric PrPSc has never been isolated.

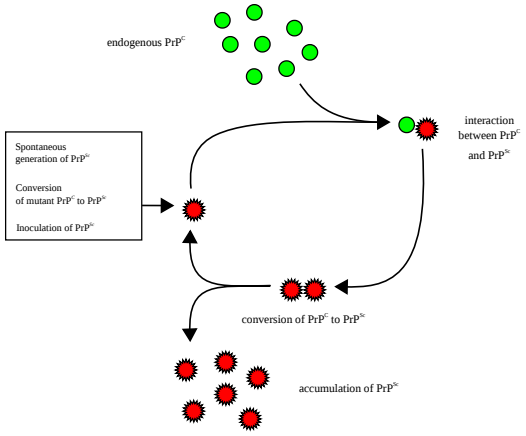

Figure: ***Diagram demonstrating how prion numbers increase****: Heterodimer model of prion propagation.*

An alternative model assumes that PrPSc exists only as fibrils, and that fibril ends bind PrPC and convert it into PrPSc. If this were all, then the quantity of prions would increase linearly, forming ever longer fibrils. But exponential growth of both PrPSc and of the quantity of infectious particles is observed during prion disease. This can be explained by taking into account fibril breakage. A mathematical solution for the exponential growth rate resulting from the combination of fibril growth and fibril breakage has been found.

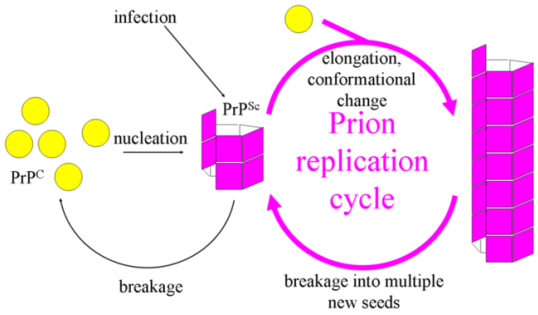

Figure: **The Fibril Model**: Illustrating prion propagation.

The protein-only hypothesis has been criticised by those who feel that the simplest explanation of the evidence to date is viral. For more than a decade, Yale University neuropathologist Laura Manuelidis has been proposing that prion diseases are caused instead by an unidentified slow virus. In January 2007, she and her colleagues published an article reporting to have found a virus in 10%, or less, of their scrapie-infected cells in culture.

The virion hypothesis states that TSEs are caused by a replicable informational molecule (likely to be a nucleic acid) bound to PrP. Many TSEs, including scrapie and BSE, show strains with specific and distinct biological properties, a feature which supporters of the virion hypothesis feel is not explained by prions.

Recent studies propagating TSE infectivity in cell-free reactions and in purified component chemical reactions strongly suggest against TSE's viral nature. Using a similar defined recipe of multiple components (PrP, POPG lipid, RNA), Jiyan Ma and colleagues generated infectious prions from recombinant PrP expressed from E. coli, casting further doubt on this hypothesis.

Key Points

- Prions are responsible for the transmissible spongiform encephalopathies in a variety of mammals, including bovine spongiform encephalopathy and Creutzfeldt–Jakob disease in humans. All known prion diseases affect the structure of neural tissue, are currently untreatable and universally fatal.

- Prions propagate by transmitting a misfolded protein state. When a prion enters a healthy organism, it induces existing, properly-folded proteins to convert into the disease-associated, prion form; it then acts as a template to guide the misfolding of more proteins into prion form.
- All known mammalian prion diseases are caused by the so-called prion protein, PrP. The endogenous, properly folded, form is denoted PrPC while the disease-linked, misfolded form is denoted PrPSc.The precise structure of the prion is not known.
- The first hypothesis to explain how prions replicate in a protein-only manner was the heterodimer model, which assumed that a single PrPSc molecule binds to a single PrPC molecule and catalyzes its conversion into PrPSc. The two PrPSc molecules then come apart and can go on to convert more PrPC.
- An alternative model assumes that PrPSc exists only as fibrils and that fibril ends bind PrPC and convert it into PrPSc. The exponential growth of both PrPSc and of the quantity of infectious particles observed during prion disease can be explained by taking fibril breakage into account.
- The protein-only hypothesis has been criticised by those who feel that the simplest explanation of the evidence to date is viral. However, recent studies propagating TSE infectivity in cell-free reactions and in purified component chemical reactions strongly suggest against TSE's viral nature.

Key Terms

- **Amyloid**: Insoluble fibrous protein aggregates sharing specific structural traits. They arise from at least 18 inappropriately folded versions of proteins and polypeptides present naturally in the body. These misfolded structures alter their proper configuration such that they erroneously interact with one another or other cell components forming insoluble fibrils. They have been associated with the pathology of more than 20 serious human diseases in that, abnormal accumulation of amyloid fibrils in organs may lead to amyloidosis, and may play a role in various neurodegenerative disorders.
- **Creutzfeldt–Jakob disease**: A degenerative neurological disorder (brain disease) that is incurable and invariably fatal. In CJD, the brain tissue develops holes and takes on a sponge-like texture, due to a type of infectious protein called a prion.
- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.

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SECTION OVERVIEW

9.7: Viral Diversity

Topic hierarchy

9.7A: Overview of Bacterial Viruses

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9.7D: Double-Stranded DNA Bacteriophages

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9.7A: Overview of Bacterial Viruses

Bacteriophages are viruses that infect bacteria and are among the most common and diverse entities in the biosphere.

Learning Objectives

- Evaluate the complexity of bacteriophages

Key Points

- Phages are obligate intracellular parasites that are able to reproduce only while infecting bacteria. Bacteriophages are comprised of proteins that encapsulate a DNA or RNA genome.
- Bacteriophages occur in over 140 bacterial or archaeal genera. They arose repeatedly in different hosts and there are at least 11 separate lines of descent. Nineteen families are currently recognised that infect bacteria and archaea.
- Phages are widely distributed in locations populated by bacterial hosts, such as soil or the intestines of animals. One of the densest natural sources for phages and other viruses is sea water.
- Bacteriophages may have a lytic cycle or a lysogenic cycle, and a few viruses are capable of carrying out both.
- To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria. This specificity means a bacteriophage can infect only certain bacteria bearing receptors to which they can bind, which in turn determines the phage's host range.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.
- **lysogeny**: the process by which a bacteriophage incorporates its nucleic acids into a host bacterium

Bacteriophages

Bacteriophages (phages) are potentially the most numerous "organisms" on Earth. They are among the most common and diverse entities in the biosphere. They are the viruses of bacteria (more generally, of prokaryotes). Phages are obligate intracellular parasites, meaning that they are able to reproduce only while infecting bacteria. Bacteriophages are comprised of proteins that encapsulate a DNA or RNA genome, and may have relatively simple or elaborate structures. Their genomes may encode as few as four genes, and as many as hundreds of genes. Phages replicate within bacteria following the injection of their genome into the cytoplasm.

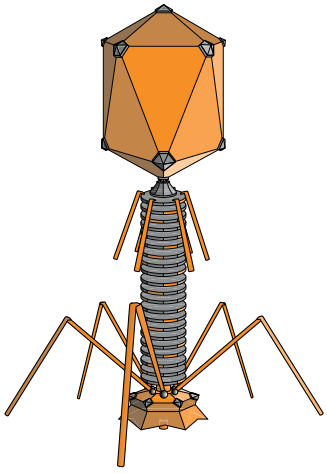

Figure: **Artistic rendering of a T4 bacteriophage**: The structure of a typical myovirus bacteriophage

Phage-ecological interactions are quantitatively vast. Bacteria (along with archaea) are highly diverse, with possibly millions of species. Phage-ecological interactions are also qualitatively diverse. There are huge numbers of environment types, bacterial-host types, and also individual phage types. Bacteriophages occur in over 140 bacterial or archaeal genera. They arose repeatedly in different hosts and there are at least 11 separate lines of descent. Over 5100 bacteriophages have been examined in the electron

microscope since 1959. Of these, at least 4950 phages (96%) have tails. Of the tailed phages 61% have long, noncontractile tails (Siphoviridae). Tailed phages appear to be monophyletic and are the oldest known virus group.

Phages are widely distributed in locations populated by bacterial hosts, such as soil or the intestines of animals. One of the densest natural sources for phages and other viruses is sea water, where up to 9×108 virions per milliliter have been found in microbial mats at the surface. Up to 70% of marine bacteria may be infected by phages.

The dsDNA tailed phages, or Caudovirales, account for 95% of all the phages reported in the scientific literature, and possibly make up the majority of phages on the planet. However, other phages occur abundantly in the biosphere, with different virions, genomes and lifestyles. Phages are classified by the International Committee on Taxonomy of Viruses (ICTV) according to morphology and nucleic acid.

Nineteen families are currently recognised that infect bacteria and archaea. Of these, only two families have RNA genomes and only five families are enveloped. Of the viral families with DNA genomes, only two have single-stranded genomes. Eight of the viral families with DNA genomes have circular genomes, while nine have linear genomes. Nine families infect bacteria only, nine infect archaea only, and one (Tectiviridae) infects both bacteria and archaea.

Bacteriophages may have a lytic cycle or a lysogenic cycle, and a few viruses are capable of carrying out both. With lytic phages such as the T4 phage, bacterial cells are broken open (lysed) and destroyed after immediate replication of the virion. As soon as the cell is destroyed, the phage progeny can find new hosts to infect.

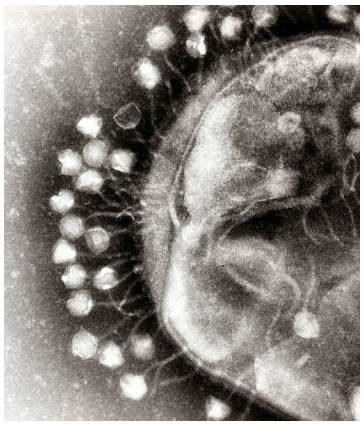

Figure: **Electron micrograph of Bacteriophages**: In this electron micrograph of bacteriophages attached to a bacterial cell, the viruses are the size and shape of coliphage T1.

In contrast, the lysogenic cycle does not result in immediate lysing of the host cell. Those phages able to undergo lysogeny are known as temperate phages. Their viral genome will integrate with host DNA and replicate along with it fairly harmlessly, or may even become established as a plasmid. The virus remains dormant until host conditions deteriorate, perhaps due to depletion of nutrients; then, the endogenous phages (known as prophages) become active. At this point they initiate the reproductive cycle, resulting in lysis of the host cell. As the lysogenic cycle allows the host cell to continue to survive and reproduce, the virus is reproduced in all of the cell's offspring. An example of a bacteriophage known to follow the lysogenic cycle and the lytic cycle is the phage lambda of E. coli.

To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella. This specificity means a bacteriophage can infect only certain bacteria bearing receptors to which they can bind, which in turn determines the phage's host range. Host growth conditions also influence the ability of the phage to attach and invade them.

Phages may be released via cell lysis, by extrusion, or, in a few cases, by budding. Lysis, by tailed phages, is achieved by an enzyme called endolysin, which attacks and breaks down the cell wall peptidoglycan. An altogether different phage type, the filamentous phages, make the host cell continually secrete new virus particles. Budding is associated with certain Mycoplasma phages.

Bacteriophage genomes are especially mosaic: the genome of any one phage species appears to be composed of numerous individual modules. These modules may be found in other phage species in different arrangements. Mycobacteriophages – bacteriophages with mycobacterial hosts – have provided excellent examples of this mosaicism. In these mycobacteriophages,

genetic assortment may be the result of repeated instances of site-specific recombination and illegitimate recombination (the result of phage genome acquisition of bacterial host genetic sequences).

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9.7B: RNA Bacteriophages

Nineteen families of bacteriophages that infect bacteria and archaea are currently recognized; of these, only two families have RNA genomes.

Learning Objectives

- Identify differences between bacterial ssRNA and dsRNA viruses

Key Points

- Cystovirus is a genus of dsRNA virus that infect certain Gram-negative bacteria. All cystoviruses are distinguished by their three strands of dsRNA and their protein and lipid outer layer. No other bacteriophage has any lipid in its outer coat.
- RNA -dependent RNA polymerases (RdRPs) are critical components in the life cycle of double-stranded RNA (dsRNA) viruses. However, it is not fully understood how these important enzymes function during viral replication.
- Bacteriophage Φ6 is a member of the Cystoviridae family that infects Pseudomonas bacteria (typically plant-pathogenic P. syringae). It is a lytic phage, though under certain circumstances has been observed to display a delay in lysis that may be described as a “carrier state”.

Key Terms

- **RNA genome**: Like DNA, RNA can carry genetic information. RNA viruses have genomes composed of RNA that encodes a number of proteins.

Nineteen families of bacteriophages that infect bacteria and archaea are currently recognized. Of these, only two families have RNA genomes: Cystoviridae (segmented dsRNA) and Leviviridae (linear ssRNA).

The Leviviridae include the genera Allolevivirus (type species: *Enterobacteria phage Qβ*) and Levivirus (type species: *Enterobacteria phage MS2*).

Cystovirus is a genus of dsRNA virus that infect certain Gram-negative bacteria. All cystoviruses are distinguished by their three strands (analogous to chromosomes) of dsRNA, totalling ~14 kb in length, and by their protein and lipid outer layer. No other bacteriophage has any lipid in its outer coat, though the Tectiviridae and the Corticoviridae have lipids within their capsids.

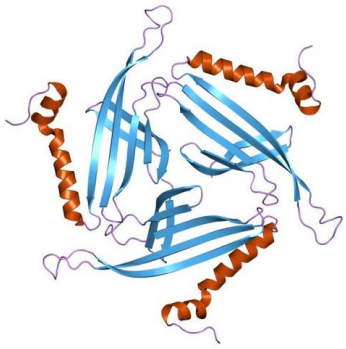

Figure: **Structure of bacteriophage PP7 from Pseudomonas aeruginosa**: Members of this protein family form the capsid of Pseudomonas phage PP7. They adopt a secondary structure consisting of a six-stranded beta sheet and an alpha helix.

Most identified cystoviruses infect Pseudomonas species, but this is likely biased due to the method of screening and enrichment. The type species is *Pseudomonas phage Φ6*, but there are many other members of this family: Φ7, Φ8, Φ9, Φ10, Φ11, Φ12, and Φ13 have been identified and named, but other cystoviruses have also been isolated.

Members of the Cystoviridae appear to be most closely related to the Reoviridae, but also share homology with the Totiviridae. Cystoviruses are the only bacteriophage that are more closely related to viruses of eukaryotes than to other phage.

Bacteriophage Φ6 is a member of the Cystoviridae family. It infects Pseudomonas bacteria (typically plant-pathogenic *P. syringae*). It has a three-part, segmented, double-stranded RNA genome, totalling ~13.5 kb in length. Φ6 and its relatives have a lipid membrane around their nucleocapsid, a rare trait among bacteriophages. It is a lytic phage, though under certain circumstances has been observed to display a delay in lysis that may be described as a “carrier state. ”

Φ6 typically attaches to the Type IV pilus of *P. syringae* with its attachment protein, P3. It is thought that the cell then retracts its pilus, pulling the phage toward the bacterium. Fusion of the viral envelope with the bacterial outer membrane is facilitated by the phage protein, P6. The muralytic (peptidoglycan-digesting) enzyme, P5, then digests a portion of the cell wall, and the nucleocapsid enters the cell coated with the bacterial outer membrane.

RNA-dependent RNA polymerases (RdRPs) are critical components in the life cycle of double-stranded RNA (dsRNA) viruses. However, it is not fully understood how these important enzymes function during viral replication. Expression and characterization of the purified recombinant RdRP of Φ6 is the first direct demonstration of RdRP activity catalyzed by a single protein from a dsRNA virus. The recombinant Φ6 RdRP is highly active in vitro, possesses RNA replication and transcription activities, and is capable of using both homologous and heterologous RNA molecules as templates.

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9.7C: Single-Stranded DNA Bacteriophages

Of the viral families with DNA genomes, only two have single-stranded genomes, the Inoviridae and the Microviridae.

Learning Objectives

- Illustrate the characteristics and life cycle of ssDNA bacteriophages

Key Points

- The Inoviridae are a family of filamentous bacteriophages. The virons are non-enveloped, rod-shaped, and filamentous. Viron release may involve host lysis, but alternatively productive infection may occur by budding from the host membrane.
- The Microviridae are a family of bacteriophages with a single-stranded DNA genome. Their genomes are among the smallest of the DNA viruses. Although the majority of species in this family have lytic life cycles, a few may have temperate life cycles.
- The Microviridae are divided into two subfamilies, Gokushovirinae and Microvirinae. These groups differ in their hosts, genome structure, and viron composition.

Key Terms

- **microviridae**: The Microviridae are a family of bacteriophages with a single-stranded DNA genome.
- **virion**: A single individual particle of a virus (the viral equivalent of a cell).

Nineteen viral families are currently recognized that infect bacteria and archaea. Of these, only two families have RNA genomes and only five are enveloped. Of the viral families with DNA genomes, only two have single-stranded genomes.

Inoviridae

The Inoviridae are a family of filamentous bacteriophages. The name of the family is derived from the Greek *nos*, meaning “muscle. ”

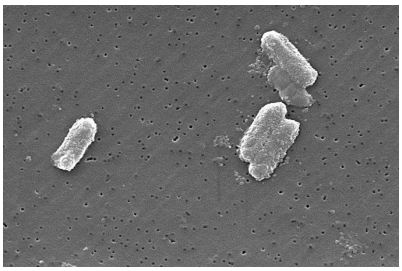

Figure: **Citrobacter freundii**: Citrobacter freundii, one member of the family Enterobacteriaceae. The genus Inovirus infect species of Enterobacteriaceae.

Taxonomy

There are two genera in this family: Inovirus and Plectrovirus. These genera differ in their host range: Plectovirii infect hosts of the class Mollicutes, while Inovirii infect species of the Enterobacteriaceae, Pseudomonadaceae, Spirillaceae, Xanthomonadaceae, Clostridium, and Propionibacterium classes.

Physical and Genomic Properties

Inoviridae are non-enveloped, rod-shaped, and filamentous. The capsid has a helical symmetry, and in general has a length of 85-280 nm or 760-1950 nm and a width of 10-16 nm or 6-8 nm, respectively. These morphological differences depend on the species.

The genomes are non-segmented, circular, positive-sense, single-stranded DNA, 4.4-8.5 kilobases in length. They encode 4 to 11 proteins. Replication of the genome occurs via a dsDNA intermediate and the rolling circle mechanism. Gene transcription is by the host’s cellular machinery, as each gene has a specific promoter.

Life Cycle

There are six steps in the life cycle of Inoviridae:

1. Adsorbion to the host via specific receptor(s)

2. Movement of the viral DNA into the host cell
3. Conversion of the single-strand form to a double-stranded intermediate
4. Replication of the viral genome
5. Synthesis of the new virions
6. Release of the new virions from the host

Action in Host

Conversion from single-stranded to double-stranded form is carried out by the host's own DNA polymerase. The host's RNA polymerase binds to the viral genome and syntheses RNA. Some of this RNA is translated and the remainder is used to initiate DNA replication.

Virion release may involve host lysis, but alternatively productive infection may occur by budding from the host membrane. This pattern is typically seen in the Plectivirus genus. A number of exceptions to this life cycle are known. Lysogenic species, which encode integrases, exist within this family.

Microviridae

The Microviridae are a family of bacteriophages with a single-stranded DNA genome. The name of this family is derived from the Greek *micro*, meaning "small. " This refers to the size of their genomes, which are among the smallest of the DNA viruses.

Taxonomy

This family is divided into two subfamilies, Gokushovirinae (derived from the Japanese for "very small") and Microvirinae. These groups differ in their hosts, genome structure, and virion composition.

Gokushoviruses are currently known to infect only obligate intra-cellular parasites. These species are members of the genera Bdellovibrio, Chlamydia, and Spiroplasma. Subfamily Microvirinae are all of the genus Microvirus. All seven such members infect Enterobacteria.

Physical and Genomic Properties

Members of the subfamily Gokushovirus have only two structural proteins: capsid proteins F (Virus Protein 1) and DNA pilot protein H (Virus Protein 2) and do not use scaffolding proteins. They also possess 'mushroom-like' protrusions positioned at the three-fold axes of symmetry of their icosahedral capsids. These are formed by large insertion loops within the protein F of gokushoviruses and are absent in the microviruses. They lack both the external scaffolding protein D and the major spike protein G of the species in the genus Microvirus. The genomes of this group tend to be smaller, about 4.5 kb in length. This subfamily includes the genera Bdellomicrovirus, Chlamydiamicrovirus, and Spiromicrovirus.

Microviridae are non-enveloped and round with an icosahedral symmetry. They have a diameter between 25-27 nanometers and lack tails. Each virion has 60 copies each of the F, G, and J proteins and 12 copies of the H protein. Viruses in this family replicate their genomes via a rolling circle mechanism and encode dedicated RCR initiation proteins. Although the majority of species in this family have lytic life cycles, a few may have temperate life cycles.

Life Cycle

There are a number of steps in the life cycle:

1. Adsorbion to the host via specific receptor(s)
2. Movement of the viral DNA into the host cell
3. Conversion of the single-strand form to a double-stranded intermediate, known as the replicative form I
4. Transcription of early genes
5. Replication of the viral genome
6. Late genes are now transcribed by the host's RNA polymerase
7. Synthesis of the new virions
8. Maturation of the virions in the host cytoplasm
9. Release from the host

Action in Host

Cell lysis is mediated by the phiX174-encoded protein E, which inhibits the peptidoglycan synthesis, leading to the eventual bursting of the infected cell.

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9.7D: Double-Stranded DNA Bacteriophages

The dsDNA tailed phages, or Caudovirales, account for 95% of all known phages and possibly make up the majority of phages on the planet.

Learning Objectives

- Describe dsDNA bacteriophages

Key Points

- The Caudovirales are an order of viruses also known as the tailed bacteriophages. The virus particles have a distinct shape; each virion has an icosohedral head that contains the viral genome, and is attached to a flexible tail by a connector protein.
- The order encompasses a wide range of viruses, many of which contain genes of similar nucleotide sequence and function. Some tailed bacteriophage genomes can vary quite significantly in nucleotide sequence, even among the same genus. There are at least 350 recognized species in this order.
- Because of the lack of homology between the amino acid and DNA sequences of these viruses, the three families here are defined based on morphology: the Myoviridae have long contractile tails, the Podoviridae have short noncontractile tails, and the Siphoviridae have long non-contractile tails.

Key Terms

- **Caudovirales**: A taxonomic order within the kingdom Virus—the bacteriophages that have tails.

The Double-Stranded DNA (dsDNA) tailed phages, or Caudovirales, account for 95% of all the phages reported in the scientific literature, and possibly make up the majority of phages on the planet. Nineteen families that infect bacteria and archaea are currently recognized; of these, 15 have double-stranded DNA genomes.

Under the Baltimore classification scheme, the Caudovirales are group I viruses as they have double-stranded DNA (dsDNA) genomes, which can be anywhere from 18,000 base pairs to 500,000 base pairs in length. The virus particles have a distinct shape; each virion has an icosohedral head that contains the viral genome, and is attached to a flexible tail by a connector protein. The order encompasses a wide range of viruses, many of which contain genes of similar nucleotide sequence and function. Some tailed bacteriophage genomes can vary quite significantly in nucleotide sequence, however, even among the same genus. Due to their characteristic structure and possession of potentially homologous genes, it is believed these bacteriophages possess a common origin. There are at least 350 recognized species in this order.

Upon encountering a host bacterium, the tail section of the virion binds to receptors on the cell surface and delivers the DNA into the cell by use of an injectisome-like mechanism (an *injectisome* is a nanomachine that evolved for the delivery of proteins by type III secretion). The tail section of the virus punches a hole through the bacterial cell wall and plasma membrane and the genome passes down the tail into the cell. Once inside, the genes are expressed from transcripts made by the host machinery, using host ribosomes. Typically, the genome is replicated by use of concatemers, in which overlapping segments of DNA are made, and then put together to form the whole genome.

Viral capsid proteins come together to form a precursor prohead, into which the genome enters. Once this has occurred, the prohead undergoes maturation by cleavage of capsid subunits to form an icosohedral phage head with 5-fold symmetry. After the head maturation, the tail is joined in one of two ways: either the tail is constructed separately and joined with the connector, or the tail is constructed directly onto the phage head. The tails consist of helix-based proteins with 6-fold symmetry. After maturation of virus particles, the cell is lysed by lysins, holins, or a combination of the two.

Because the lack of homology between the amino acid and DNA sequences of these viruses precludes these from being used as taxonomic markers (as is common for other organisms), the three families here are defined on the basis of morphology. This classification scheme was originated by Bradley in 1969 and has since been extended. All viruses in this order have icosahedral or oblate heads, but differ in the length and contractile abilities of their tails. The Myoviridae have long tails that are contractile, the Podoviridae have short noncontractile tails, and the Siphoviridae have long non-contractile tails. Siphoviridae constitute the majority of the known tailed viruses.

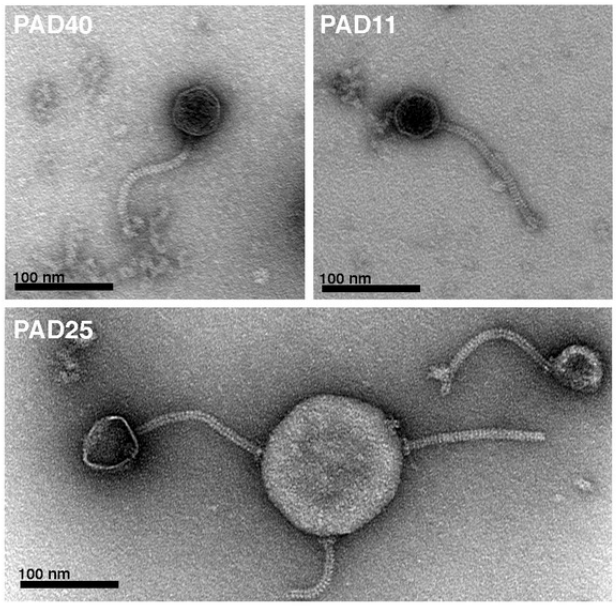

Figure: **Siphovirus phages**: Electron micrographs of bacteriophages from P. acnes. Phages were negatively stained with 0.75% uranyl formate and subjected to transmission electron microscopy. The phages have a head of approximately 55 nm in diameter, loaded with genetic material. Their tails have a size of 150 × 10 nm and are flexible and non-contractile. In the lower micrograph, PAD25 is adhering to bacterial cell debris, and two phages have lost their heads. At the attachment site between the phage and the cell debris, a base plate with attached spikes can be observed. All phages were classified as Siphoviruses based on their morphology.

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9.7E: Mu: A Double-Stranded Transposable DNA Bacteriophage

Bacteriophage Mu is a temperate bacteriophage that uses DNA-based transposition in its lysogenic cycle.

Learning Objectives

- Outline the life cycle of Mu phages

Key Points

- All of the known temperate phages employ one of only three different systems for their lysogenic cycle: lambda-like integration/excision, Mu-like transposition, or the plasmid-like partitioning of phage N15.
- Phage Mu uses DNA -based transposition to integrate its genome into the genome of the host cell that it is infecting. It can then use transposition to initiate its viral DNA replication.
- Mu phage transposition is the best-known example of replicative transposition. Its transposition mechanism is somewhat similar to a homologous recombination.

Key Terms

- **replicative transposition**: A mechanism of transposition in which the transposable element is duplicated during the reaction, so that the transposing entity is a copy of the original element.

Bacteriophage Mu, or phage Mu, is a temperate bacteriophage, a type of virus that infects bacteria. It belongs to the family Myoviridae, and consists of an icosahedral head, a contractile tail, and six tail fibers.

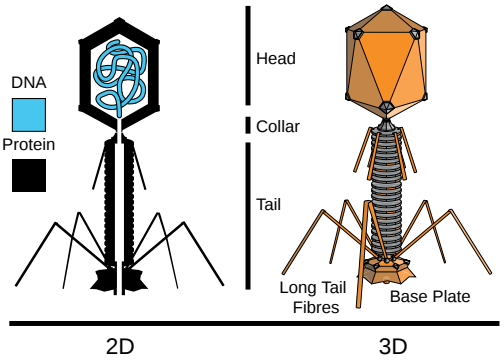

Figure: **Myoviridae**: Structural overview of the T4 phage, from the same family (Myoviridae) as Mu bacteriophage.

All of the known temperate phages employ one of only three different systems for their lysogenic cycle: lambda-like integration/excision, Mu-like transposition, or the plasmid-like partitioning of phage N15.

Mu bacteriophage uses DNA-based transposition to integrate its genome into the genome of the host cell that it is infecting. It can then use transposition to initiate its viral DNA replication. Once the viral DNA is inserted into the bacteria, the Mu's transposase protein/enzyme in the cell recognizes the recombination sites at the ends of the viral DNA (gix-L and gix-R sites) and binds to them, allowing the process of replicating the viral DNA or embedding it into the host genome. A transposable element (TE) is a DNA sequence that can change its relative position (self-transpose) within the genome of a single cell. The mechanism of transposition can be either "copy and paste" or "cut and paste. " Transposition can create phenotypically significant mutations and alter the cell's genome size.

Mu phage transposition is the best known example of replicative transposition. Its transposition mechanism is somewhat similar to a homologous recombination. Replicative transposition is a mechanism of transposition in molecular biology, proposed by James A. Shapiro in 1979, in which the transposable element is duplicated during the reaction, so that the transposing entity is a copy of the original element. In this mechanism, the donor and receptor DNA sequences form a characteristic intermediate "theta" configuration, sometimes called a "Shapiro intermediate. " Replicative transposition is characteristic to retrotransposons and occurs from time to time in class II transposons.

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9.7F: Virulent Bacteriophages and T4

T-4 bacteriophage is a virulent bacteriophage that infects E. coli bacteria; virulent bacteriophages have a lytic life cycle.

Learning Objectives

- Summarize how the T4 life cycle serves as a model for viral virulence

Key Points

- Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism is determined by its virulence factors.
- A key difference between the lytic and lysogenic phage cycles is that in the lytic phage, the viral DNA exists as a separate molecule within the bacterial cell, and replicates separately from the host bacterial DNA.
- The T-4's tail fibres allow attachment to a host cell, and the T4's tail is hollow so that it can pass its nucleic acid to the cell it is infecting during attachment. T4 is capable of undergoing only a lytic lifecycle and not the lysogenic lifecycle.

Key Terms

- **lytic cycle**: The normal process of viral reproduction involving penetration of the cell membrane, nucleic acid synthesis, and lysis of the host cell.
- **virulence**: the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host.

Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism is determined by its virulence factors. Virus virulence factors determine whether an infection will occur and how severe the resulting viral disease symptoms are. Viruses often require receptor proteins on host cells to which they specifically bind. Typically, these host cell proteins are endocytosed and the bound virus then enters the host cell. Virulent viruses such as HIV, which causes AIDS, have mechanisms for evading host defenses.

Some viral virulence factors confer ability to replicate during the defensive inflammation responses of the host such as during virus-induced fever. Many viruses can exist inside a host for long periods during which little damage is done. Extremely virulent strains can eventually evolve by mutation and natural selection within the virus population inside a host. The term "neurovirulent" is used for viruses such as rabies and herpes simplex which can invade the nervous system and cause disease there.

Model organisms of virulent viruses that have been extensively studied include virus T4 and other T-even bacteriophages which infect Escherichia coli and a number of related Bacteria.

The lytic cycle is one of the two cycles of viral reproduction, the other being the lysogenic cycle. The lytic cycle is typically considered the main method of viral replication, since it results in the destruction of the infected cell. A key difference between the lytic and lysogenic phage cycles is that in the lytic phage, the viral DNA exists as a separate molecule within the bacterial cell, and replicates separately from the host bacterial DNA. The location of viral DNA in the lysogenic phage cycle is within the host DNA, therefore in both cases the virus/phage replicates using the host DNA machinery, but in the lytic phage cycle, the phage is a free floating separate molecule to the host DNA.

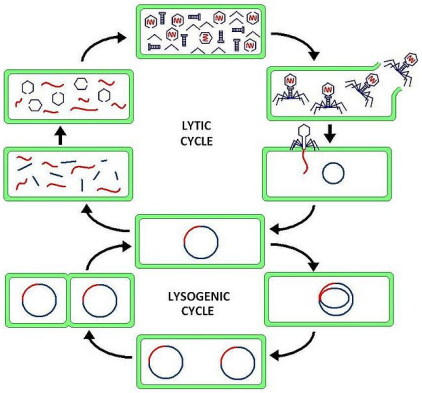

Figure: **Cycles of viral reproduction**: Comparison of the bacteriophage lysogenic and lytic cycles.

The lytic cycle is a six-stage cycle. In the first stage, called “penetration,” the virus injects its own nucleic acids into a host cell. Then the viral acids form a circle in the center of the cell. The cell then mistakenly copies the viral acids instead of its own nucleic acids. Then the viral DNA organize themselves as viruses inside the cell. When the number of viruses inside becomes too much for the cell to hold, the membrane splits and the viruses are free to infect other cells. Some viruses escape the host cell without bursting the cell membrane; instead, they bud off from it by taking a portion of the membrane with them. Because it otherwise is characteristic of the lytic cycle in other steps, it still belongs to this category, although it is sometimes named the Productive Cycle. HIV, influenza and other viruses that infect eukaryotic organisms generally use this method.

T-4 bacteriophage is a bacteriophage that infects E. coli bacteria. Its double-stranded DNA genome is about 169 kbp long and is held in an icosahedral head, also known as a capsid. T4 is a relatively large phage, at approximately 90 nm wide and 200 nm long (most phages range from 25 to 200 nm in length). Its tail fibres allow attachment to a host cell, and the T4’s tail is hollow so that it can pass its nucleic acid to the cell it is infecting during attachment. T4 is capable of undergoing only a lytic lifecycle and not the lysogenic lifecycle.

The T4 Phage initiates an E. coli infection by recognizing cell surface receptors of the host with its long tail fibers (LTF). A recognition signal is sent through the LTFs to the baseplate. This unravels the short tail fibers (STF) that bind irreversibly to the E. coli cell surface. The baseplate changes conformation and the tail sheath contracts causing GP5 at the end of the tail tube to puncture the outer membrane of the cell. The lysozyme domain of GP5 is activated and degrades the periplasmic peptidoglycan layer. The remaining part of the membrane is degraded and then DNA from the head of the phage can travel through the tail tube and enter the E. coli.

The lytic lifecycle (from entering a bacterium to its destruction) takes approximately 30 minutes (at 37 °C) and consists of:

- Adsorption and penetration (starting immediately)
- Arrest of host gene expression (starting immediately)
- Enzyme synthesis (starting after 5 minutes)
- DNA replication (starting after 10 minutes)
- Formation of new virus particles (starting after 12 minutes)

After the life cycle is complete, the host cell bursts open and ejects the newly built viruses into the environment, destroying the host cell. T4 has a burst size of approximately 100-150 viral particles per infected host. Complementation, deletion, and recombination tests can be used to map out the rII gene locus by using T4. These bacteriophage infect a host cell with their information and then blow up the host cell, thereby propagating themselves.

The T4 phage has some unique features, including:

- Eukaryote-like introns
- High speed DNA copying mechanism, with only 1 error in 300 copies
- Special DNA repair mechanisms
- It infects E. coli O157:H7

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9.7G: Temperate Bacteriophages - Lambda and P1

In virology, temperate refers to the ability of some bacteriophages to display a lysogenic life cycle.

Learning Objectives

- Evaluate the differences between the temperate phages, P1, and lambda

Key Points

- Many temperate phages can integrate their genomes into their host bacterium ‘s chromosome, together becoming a lysogen as the phage genome becomes a prophage. A temperate phage is also able to undergo a productive, typically-lytic life cycle.
- P1 is a temperate bacteriophage (phage) that infects Escherichia coli and some other bacteria. A unique feature of phage P1 is that during lysogeny its genome is not incorporated into the bacterial chromosome, as is commonly observed during lysogeny of other bacteriophage.
- Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species Escherichia coli.
- With the infection of a bacteria by phage, a lytic cycle usually ensues where the lambda DNA is replicated many times and the genes for head, tail, and lysis proteins are expressed. Under certain conditions the phage DNA may integrate itself into the host cell chromosome in the lysogenic pathway.

Key Terms

- **lytic life cycle**: One of the two cycles of viral reproduction (the other being the lysogenic cycle). The lytic cycle is typically considered the main method of viral replication and it results in the destruction of the infected cell.
- **temperate bacteriophage**: Phages able to undergo lysogeny.

In virology, temperate refers to the ability of some bacteriophages (notable coliphage λ) to display a lysogenic life cycle. Many (but not all) temperate phages can integrate their genomes into their host bacterium’s chromosome, together becoming a lysogen as the phage genome becomes a prophage. A temperate phage is also able to undergo a productive, typically-lytic life cycle, where the prophage is expressed, replicates the phage genome, and produces phage progeny, which then leave the bacterium. With phage the term *virulent* is often used as an antonym to *temperate*, but more strictly a virulent phage is one that has lost its ability to display lysogeny through mutation, rather than a phage lineage with no genetic potential to ever display lysogeny (which more properly would be described as an obligately lytic phage).

P1 is a temperate bacteriophage (phage) that infects *Escherichia coli* and some other bacteria. When undergoing a lysogenic cycle, the phage genome exists as a plasmid in the bacterium, unlike other phages (e.g., the lambda phage) that integrate into the host DNA. P1 has an icosahedral “head” containing the DNA, attached to a contractile tail with six tail fibers.

The virion is similar in structure to the T4 phage, but simpler. It has an icosahedral head containing the genome attached at one vertex to the tail. The tail has a tube surrounded by a contractile sheath, and ends in a base plate with six tail fibers. The tail fibers are involved in attaching to the host and providing specificity.

At around 93Kbp in length, the genome of the P1 phage is moderately large compared to the genomes of others, like T4 (169Kbp), lambda (48Kbp), and Ff (6.4Kbp). In the viral particle it is in the form of a linear double-stranded DNA molecule. Once inserted into the host, it circularizes and replicates as a plasmid.

Temperate phage, such as P1, have the ability to exist within the bacterial cell they infect in two different ways. In lysogeny, P1 can exist within a bacterial cell as a circular DNA, in that it exists by replicating as if it were a plasmid and does not cause cell death. Alternatively, in its lytic phase, P1 can promote cell lysis during growth, resulting in host cell death. During lysogeny, new phage particles are not produced. In contrast, during lytic growth many new phage particles are assembled and released from the cell. By alternating between these two modes of infection, P1 can survive during extreme nutritional conditions that may be imposed upon the bacterial host in which it exists.

A unique feature of phage P1 is that during lysogeny its genome is not incorporated into the bacterial chromosome, as is commonly observed during lysogeny of other bacteriophage. Instead, P1 exists independently within the bacterial cell, much like a plasmid would. P1 replicates as a 90 kilobase (kb) plasmid in the lysogenic state and is partitioned equally into two new daughter cells during normal cell division.

Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species *Escherichia coli*. This virus is temperate and may reside within the genome of its host through lysogeny.

Lambda phage consists of a virus particle including a head (also known as a capsid), a tail, and tail fibers. The head contains the phage's double-stranded circular DNA genome. The phage particle recognizes and binds to its host, *E. coli*, causing DNA in the head of the phage to be ejected through the tail into the cytoplasm of the bacterial cell. Usually, a "lytic cycle" ensues, where the lambda DNA is replicated many times and the genes for head, tail, and lysis proteins are expressed. This leads to assembly of multiple new phage particles within the cell and subsequent cell lysis, releasing the cell contents, including virions that have been assembled, into the environment. However, under certain conditions the phage DNA may integrate itself into the host cell chromosome in the lysogenic pathway. In this state, the λ DNA is called a prophage and stays resident within the host's genome without apparent harm to the host. The host can be termed a lysogen when a prophage is present.

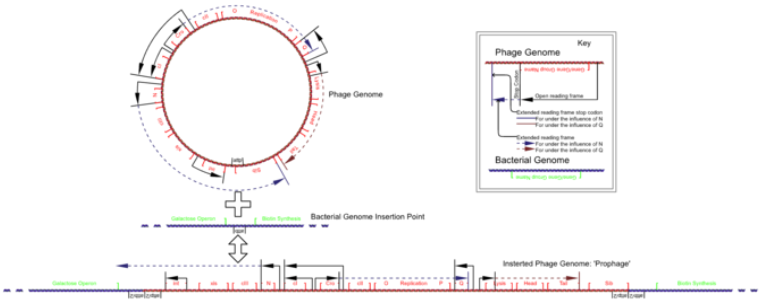

Figure: **Insertion of the bacteriophage lambda**: Schematic representation of the insertion of the bacteriophage lambda. Note how sib is displaced by the recombination event from the N extended PL promoter open reading frame.

The virus particle consists of a head and a tail that can have tail fibers. The head contains 48,490 base pairs of double-stranded, linear DNA, with 12-base single-stranded segments at both 5′ ends. These two single-stranded segments are the "sticky ends" of what is called the cos site. The cos site circularizes the DNA in the host cytoplasm. In its circular form, the phage genome therefore is 48,502 base pairs in length. The prophage exists as a linear section of DNA inserted into the host chromosome.

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9.7H: Viruses of Archaea

Learning Objectives

- Illustrate the typical characteristics of archaea-infecting viruses

A virus infecting archaea was first described in 1974. Several others have been described since then. Most have head-tail morphologies and linear double-stranded DNA genomes. Other morphologies have also been described including spindle shaped, rod shaped, filamentous, icosahedral, and spherical. Additional morphological types may exist.

Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes. These viruses have been studied in the most detail in thermophilics, particularly the orders Sulfolobales and Thermoproteales. Two groups of single-stranded DNA viruses that infect archaea have been recently isolated. One group is exemplified by the Halorubrum pleomorphic virus 1 ("Pleolipoviridae") infecting halophilic archaea and the other one by the Aeropyrum coil-shaped virus.

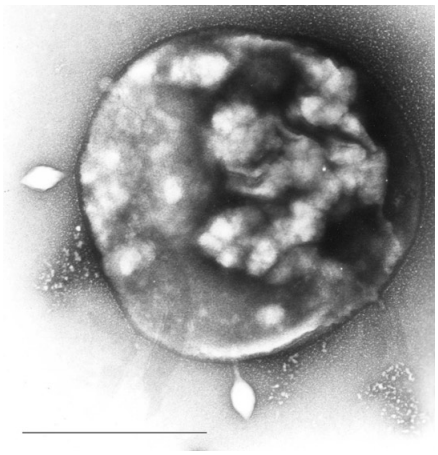

Figure: **Archaeal viral infection**: Cell of Sulfolobus infected by virus STSV1 observed under microscopy. Two spindle-shaped viruses were being released from the host cell. The strain of Sulfolobus and STSV1 (Sulfolobus tengchongensis Spindle-shaped Virus 1) were isolated by Xiaoyu Xiang and his colleagues in an acidic hot spring in Yunnan Province, China. At present, STSV1 is the largest archaeal virus to have been isolated and studied. Its genome sequence has been sequenced.

Double-stranded DNA viruses infecting archaea:

- Bacteriophages (viruses infecting bacteria) belonging to the families Tectiviridae and Corticoviridae have a lipid bilayer membrane inside the icosahedral protein capsid and the membrane surrounds the genome. The crenarchaeal virus Sulfolobus turreted icosahedral virus has a similar structure.
- Species of the order Ligamenvirales and the families Ampullaviridae, Bicaudaviridae, Clavaviridae, Fuselloviridae, Globuloviridae, and Guttaviridae infect hyperthermophilic archaea species of the Crenarchaeota.
- Species of the genus Salterprovirus infect halophilic archaea species of the Euryarchaeota.

Single-stranded DNA viruses infecting archaea:

Although around 50 archaeal viruses are known, all but two have double stranded genomes. The first archaeal ssDNA virus to be isolated is the Halorubrum pleomorphic virus 1, which has a pleomorphic enveloped virion and a circular genome. Defenses against these viruses may involve RNA interference from repetitive DNA sequences that are related to the genes of the viruses.

The second single stranded DNA virus infecting Archaea is Aeropyrum coil-shaped virus (ACV). The genome is circular and with 24,893 nucleotides is currently the largest known ssDNA genome. The viron is nonenveloped, hollow, cylindrical, and formed from a coiling fiber. The morphology and the genome appear to be unique. ACV has been suggested to represent a new viral family tentatively called "Spiraviridae" (from Latin spira, "a coil"). The Aeropyrum coil-shaped virus infects a hyperthermophilic (optimal growth at 90-95°C) host. Notably, the latter virus has the largest currently reported ssDNA genome.

Key Points

- Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes. These viruses have been studied in most detail in thermophilics, particularly the orders Sulfolobales and Thermoproteales.
- Although around 50 archaeal viruses are known, all but two have double stranded genomes; two groups of single-stranded DNA viruses that infect archaea have been recently isolated.
- Defenses against these ssDNA viruses may involve RNA interference from repetitive DNA sequences that are related to the genes of the viruses.

Key Terms

- **DNA virus**: A DNA virus is a virus that has DNA as its genetic material and replicates using a DNA-dependent DNA polymerase. The nucleic acid is usually double-stranded DNA (dsDNA) but may also be single-stranded DNA (ssDNA).

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SECTION OVERVIEW

9.8: Positive-Strand RNA Viruses in Animals

Topic hierarchy

9.8A: Positive-Strand RNA Viruses of Animals

9.8B: Virus Attachment and Genome Entry

9.8C: Viral Replication and Gene Expression

9.8D: Viral Exit

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9.8A: Positive-Strand RNA Viruses of Animals

Positive-Strand RNA Viruses of Animals

Positive strand RNA viruses are the single largest group of RNA viruses with 30 families.

LEARNING OBJECTIVES

Categorize the characteristics of positive-strand viruses

KEY TAKEAWAYS

Key Points

- Nucleic acid is usually single-stranded RNA (ssRNA), but may be double-stranded RNA (dsRNA).
- An RNA virus is a virus that has RNA (ribonucleic acid) as its genetic material.
- Notable human diseases caused by RNA viruses include SARS, influenza, hepatitis C, West Nile fever, and polio.

Key Terms

- **virus**: A submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat. It requires a living cell to replicate, and often causes disease in the host organism.
- **genetic**: Relating to genetics or genes.
- **RNA**: Ribonucleic acid (RNA) is a ubiquitous family of large biological molecules that performs multiple vital roles in the coding, decoding, regulation, and expression of genes.

Single stranded RNA viruses can be classified according to the sense or polarity of their RNA into negative-sense and positive-sense, or ambisense RNA viruses. Positive-sense viral RNA is similar to mRNA and thus can be immediately translated by the host cell. Negative-sense viral RNA is complementary to mRNA and thus must be converted to positive-sense RNA by an RNA polymerase before translation. As such, purified RNA of a positive-sense virus can directly cause infection though it may be less infectious than the whole virus particle. Purified RNA of a negative-sense virus is not infectious by itself as it needs to be transcribed into positive-sense RNA; each virion can be transcribed to several positive-sense RNAs. Ambisense RNA viruses resemble negative-sense RNA viruses, except they also translate genes from the positive strand. A common viral positive-strand RNA viruses that infect humans are the picornaviruses.



Figure: **Foot and Mouth Disease**: Foot and Mouth Disease is caused by the Aphthovirus virus which positive-strand RNA virus, of the Picornaviridae family of animal viruses.

A picornavirus is a virus belonging to the family Picornaviridae. Picornaviruses are non-enveloped, positive-stranded RNA viruses with an icosahedral capsid. The genome RNA is unusual because it has a protein on the 5′ end that is used as a primer for transcription by RNA polymerase. The name is derived from pico, meaning small, and RNA, referring to the ribonucleic acid genome, so “picornavirus” literally means small RNA virus. Picornaviruses are separated into a number of genera and include many important pathogens of humans and animals. The diseases they cause are varied, ranging from acute “common-cold”-like illnesses, to poliomyelitis, to chronic infections in livestock. Additional species not belonging to any of the recognized genera continue to be described.

Picornaviruses are separated into a number of genera. Contained within the picornavirus family are many organisms of importance as vertebrate and human pathogens, shown in the table below.Enteroviruses infect the enteric tract, which is reflected in their name. On the other hand, rhinoviruses infect primarily the nose and the throat. Enteroviruses replicate at 37°C, whereas rhinoviruses grow better at 33°C, as this is the lower temperature of the nose. Enteroviruses are stable under acid conditions and thus they are able to survive exposure to gastric acid. In contrast, rhinoviruses are acid-labile (inactivated or destroyed by low pH conditions) and that is the reason why rhinovirus infections are restricted to the nose and throat.

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9.8B: Virus Attachment and Genome Entry

Attachment is a specific binding between viral capsid proteins and specific receptors on the host cellular surface.

Learning Objectives

- Differentiate virus attachment and genome entry

Key Points

- Viral entry is the earliest stage of infection in the viral life cycle, as the virus comes into contact with the host cell and introduces viral material into the cell.
- Attachment to the receptor can induce the viral envelope protein to undergo changes that results in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.
- Virions enter the host cell through receptor-mediated endocytosis or membrane fusion.

Key Terms

- **capsid**: The outer protein shell of a virus.
- **receptors**: In the field of biochemistry, a receptor is a molecule most often found on the surface of a cell, which receives chemical signals originating externally from the cell.
- **virions**: An entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid.

Viral populations do not grow through cell division, because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell. The life cycle of viruses differs greatly between species, but they all share the same basic life cycle stages.

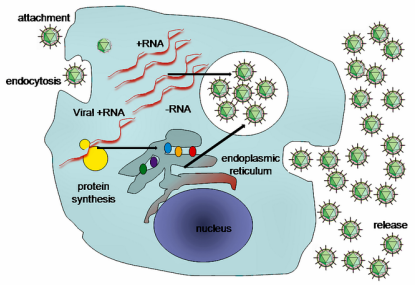

Figure: **A typical virus replication cycle**: There are six basic stages in the life cycle of viruses: attachment, penetration, uncoating, replication, assembly of viral particles, and release.

Attachment is a specific binding between viral capsid proteins and specific receptors on the host cellular surface. This specificity determines the host range of a virus. For example, HIV infects a limited range of human leukocytes. This is because its surface protein, gp120, specifically interacts with the CD4 molecule, a chemokine receptor, which is most commonly found on the surface of CD4+ T-Cells. This mechanism has evolved to favor those viruses that infect only cells in which they are capable of replication. Attachment to the receptor can induce the viral envelope protein to undergo changes that results in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.

Penetration follows attachment: Virions enter the host cell through receptor-mediated endocytosis or membrane fusion. This is often called “viral entry. ” The infection of plant and fungal cells is different from that of animal cells. Plants have a rigid cell wall made of cellulose, and fungi one of chitin, so most viruses can get inside these cells only after trauma to the cell wall. However, nearly all plant viruses (such as tobacco mosaic virus) can also move directly from cell to cell, in the form of single-stranded nucleoprotein complexes, through pores called “plasmodesmata”. Bacteria, such as plants, have strong cell walls that a virus must breach to infect the cell. However, given that bacterial cell walls are less thick than plant cell walls due to their much smaller size, some viruses have evolved mechanisms that inject their genome into the bacterial cell across the cell wall, while the viral capsid remains outside

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9.8C: Viral Replication and Gene Expression

RNA viruses are classified into distinct groups depending on their genome and mode of replication.

Learning Objectives

- Examine viral gene expression during virus replication

Key Points

- Positive sense, negative sense, double stranded viruses, and retroviruses are RNA viruses with different modes of replication.
- Positive-sense ssRNA viruses (Group IV) have their genome directly utilized as if it were mRNA.
- Replication of viruses involves primarily multiplication of the genome.
- The polarity of single-stranded RNA viruses largely determines the replicative mechanism.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.
- **virus**: A submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat. It requires a living cell to replicate, and often causes disease in the host organism.
- **replication**: Process by which an object, person, place or idea may be copied mimicked or reproduced.

Replication of viruses primarily involves the multiplication of the viral genome. Replication also involves synthesis of viral messenger RNA (mRNA) from “early” genes (with exceptions for positive sense RNA viruses), viral protein synthesis, possible assembly of viral proteins, then viral genome replication mediated by early or regulatory protein expression. This may be followed, for complex viruses with larger genomes, by one or more further rounds of mRNA synthesis: “late” gene expression is, in general, necessary for structural or virion proteins. Viral replication usually takes place in the cytoplasm.

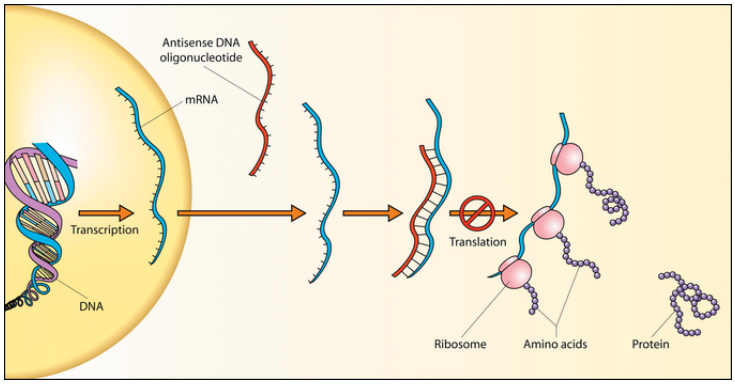

Figure: **DNA to RNA to protein**: Schematic showing how antisense DNA strands can interfere with protein translation.

Viruses that replicate via RNA intermediates need an RNA-dependent RNA- polymerase to replicate their RNA, but animal cells do not seem to possess a suitable enzyme. Therefore, this type of animal RNA virus needs to code for an RNA-dependent RNA polymerase. No viral proteins can be made until viral messenger RNA is available; thus, the nature of the RNA in the virion affects the strategy of the virus: In plus-stranded RNA viruses, the virion (genomic) RNA is the same sense as mRNA and so functions as mRNA. This mRNA can be translated immediately upon infection of the host cell. Examples: poliovirus (picornavirus), togaviruses, and flaviviruses.

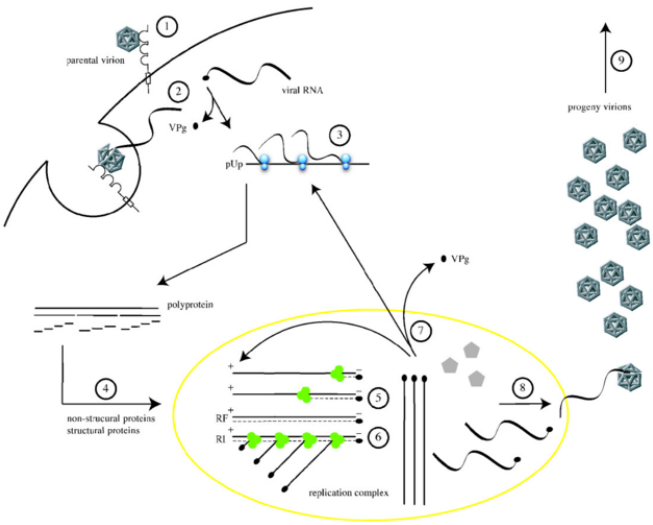

Figure: **The replication cycle of poliovirus**: The cellular life cycle of poliovirus. It is initiated by binding of a poliovirion to the cell surface macromolecule CD155, which functions as the receptor (1). Uncoating of the viral RNA is mediated by receptor-dependent destabilization of the virus capsid (2). Cleavage of the viral protein VPg is performed by a cellular phosphodiesterase, and translation of the viral RNA occurs by a cap-independent (IRES-mediated) mechanism (3). Proteolytic processing of the viral polyprotein yields mature structural and non-structural proteins (4). The positive-sense RNA serves as template for complementary negative-strand synthesis, thereby producing a double-stranded RNA (replicative form, RF) (5). Initiation of many positive strands from a single negative strand produces the partially single-stranded replicative intermediate (RI) (6). The newly synthesized positive-sense RNA molecules can serve as templates for translation (7) or associate with capsid precursors to undergo encapsidation and induce the maturation cleavage of VP0 (8), which ultimately generates progeny virions. Lysis of the infected cell results in release of infectious progeny virions (9).

RNA viruses are classified into distinct groups depending on their genome and mode of replication (and the numerical groups based on the older Baltimore classification).

Positive-sense ssRNA viruses (Group IV) have their genome directly utilized as if it were mRNA, with host ribosomes translating it into a single protein which is modified by host and viral proteins to form the various proteins needed for replication. One of these includes RNA-dependent RNA polymerase (RNA replicase), which copies the viral RNA to form a double-stranded replicative form, in turn this directs the formation of new virions.

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9.8D: Viral Exit

Viruses are released from the host cell following assembly.

Learning Objectives

- Explain how viruses exit host cells

Key Points

- Once replication has been completed and the host cell is exhausted of all resources in making viral progeny, the viruses may begin to leave the cell by several methods.
- Viral exit methods include budding, exocytosis, and cell lysis.
- Budding through the cell envelope, in effect using the cell's membrane for the virus itself is most effective for viruses that need an envelope.
- This process will slowly use up the cell membrane and eventually lead to the demise of the cell.

Key Terms

- **exocytosis**: The secretion of substances through cellular membranes, either to excrete waste products or as a regulatory function
- **lysogenic**: Of, relating to, or causing lysis.
- **virions**: An entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid.

Viral populations do not grow through cell division because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell. The life cycle of viruses differs between species, but follows the same basic stages.

Viruses can be released from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present. This is a feature of many bacterial and some animal viruses. Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host's chromosome. The viral genome is then known as a " provirus " or, in the case of bacteriophages a "prophage. " Whenever the host divides, the viral genome is also replicated. The viral genome is mostly silent within the host. However, at some point, the provirus or prophage may give rise to active virus, which may lyse the host cells. Enveloped viruses (e.g., HIV) typically are released from the host cell by budding. During this process the virus acquires its envelope, which is a modified piece of the host's plasma or other, internal membrane.

Viral shedding refers to the successful reproduction, expulsion, and host-cell infection caused by virus progeny. Once replication has been completed and the host cell is exhausted of all resources in making viral progeny, the viruses may begin to leave the cell by several methods.

Different types of virus have varying sites of synthesis and replication. For example, synthesis and replication for DNA viruses occur in the cell's nucleus while it is usually the cytoplasm for RNA viruses. Virus assembly depends on the site of synthesis and such sites are the nucleus, endoplasmic reticulum, and the Golgi apparatus aka Golgi body. Aside from this, assembly also occurs in the viroplasm which is an inclusion body in a cell. When the virus has replicated and multiplied, they would want to leave the infected cell and infect other cells. However, they require an envelope to enclose the DNA as well as to bind with the other healthy cells so that they can infect. The viral envelope is the typical lipid bilayer, derived from the host cell itself and sources usually come from the nuclear membrane, endoplasmic reticulum, Golgi apparatus/body, and plasma membrane. It also depends on where the virus 'bud' off from the host.

Budding is a method which viruses use to exit the cell. "Budding" through the cell envelope, in effect using the cell's membrane for the virus itself is most effective for viruses that need an envelope in the first place. These include enveloped viruses such as HSV, SARS, or smallpox. Prior to budding, the virus may put its own receptor onto the surface of the cell in preparation for the virus to bud through, forming an envelope with the viral receptors already on it. This process will slowly use up the cell membrane and eventually lead to the demise of the cell. This is also how antiviral responses are able to detect virus infected cells.

Other methods for exit would be cell lysis. This method releases the virus from the infected cell by bursting its membrane and this kills the cell as well. Another method is by accumulating the virus particles in vesicles and releasing them via exocytosis. Exocytosis is the process where vesicles containing the virus are secreted/excreted out of the infected cell.

Positive-strand RNA mature virions are infectious. Virions are released following cell lysis. Excess capsids are formed and inclusion bodies may be seen in the cytoplasm.

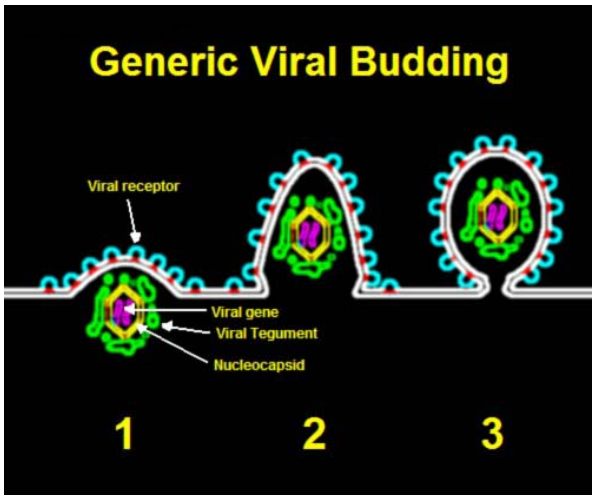

Figure: **Generic Viral Budding**: Viral budding uses the host's cell membrane eventually causing cell death.

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SECTION OVERVIEW

9.9: Negative-Strand RNA Viruses in Animals

Topic hierarchy

9.9A: Negative-Strand RNA Viruses of Animals

9.9B: Attachment and Entry to the Host Cell

9.9C: Replicative Cycle of Influenza A

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9.9A: Negative-Strand RNA Viruses of Animals

Negative-strand RNA viruses are single-stranded viruses that can infect several types of animals.

Learning Objectives

- Explain the mechanism of genome replication in negative-strand RNA viruses

Key Points

- Negative-strand RNA viruses can infect animals, but in several cases they can go from animals into humans, such as the SARS virus of the Ebola Zaire virus.
- The viron RNA is negative sense (complementary to mRNA and cannot encode proteins), which means it must be replciated over to mRNA before protein production can begin. This is carried out by an RNA-dependent RNA-polymerase.
- Negative-strand viruses can be found in many niches of Earth and are responsible for many common and very deleterious diseases of animals.

Key Terms

- **SARS**: The SARS coronavirus, sometimes shortened to SARS-CoV, is the virus that causes severe acute respiratory syndrome (SARS).
- **RNA-dependent RNA-polymerase**: (RdRP, or RNA replicase) An enzyme that catalyzes the replication of RNA from an RNA template. This is in contrast to a typical DNA-dependent RNA polymerase, which catalyzes the transcription of RNA from a DNA template.

The study of animal viruses is important from a veterinary viewpoint, but many animal viruses are also important from a human medical perspective. The emergence of the SARS virus or Ebola Zaire virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. In addition, research into animal viruses has made an important contribution to our understanding of viruses in general, including their replication, molecular biology, evolution, and interaction with the host. Animal RNA viruses can be classified according to the sense or polarity of their RNA into negative-sense, positive-sense, or ambisense RNA viruses.

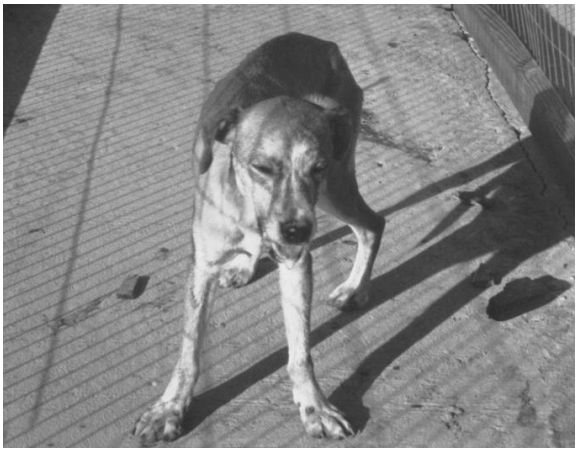

Figure: **Rabies**: Note the salivia dripping from the dog's mouth, a typical sign of a rabies infection. The infection of domestic animals with rabies was common until the 1960s; now most instances of rabies-infected animals are found in the wild.

The RNA found in a negative-sense virus is not infectious by itself, as it needs to be transcribed into positive-sense RNA. The complementary plus-sense mRNA must be made before proteins can be translated from the viral genome. This RNA negative-strand to positive-strand copying is carried out by an RNA-dependent RNA-polymerase. Each virion that has one negative-strand copy can be transcribed to several positive-sense RNAs. There are several different types of negative-strand RNA viruses that infect animals; two families will be discussed here in further detail.

Rhabdoviruses are a diverse family of single-stranded, negative-sense RNA viruses that can successfully utilize a myriad of ecological niches, ranging from plants and insects, to fish and mammals. This virus family includes pathogens —the rabies virus, vesicular stomatitis virus, potato yellow dwarf virus, etc.—that are of tremendous public health, veterinary, and agricultural

significance. Due to the relative simplicity of their genomes and morphology, in recent years rhabdoviruses have become powerful model systems for studying molecular virology.

Paramyxoviruses are a diverse family of non-segmented negative-strand RNA viruses that include many highly pathogenic viruses affecting humans, animals, and birds. In recent years the advent of reverse genetics has led to a greater understanding of their genomics, molecular biology, and viral pathogenesis. Paramyxoviruses cause a range of diseases in animal species: canine distemper virus (dogs), phocine distemper virus (seals), cetacean morbillivirus (dolphins and porpoises), Newcastle disease virus (birds), and rinderpest virus (cattle). Some paramyxoviruses, such as the henipaviruses, are zoonotic pathogens, occurring naturally in an animal host, but also able to infect humans.

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9.9B: Attachment and Entry to the Host Cell

For influenza viral propagation to begin, there first must be viron attachment and entry into a host cell.

Learning Objectives

- Explain the role of hemagglutinin in the attachment and entry processes of influenza virus

Key Points

- A glycoprotein on the surface of a virus recognizes a receptor on a host, beginning the attachment process.
- After attachment, the influenza virus is brought into the host cell through an endosome. The low pH of the endosome breaks down the viral capsid and releases the viral contents into the cell.
- A well-described example of this is the influenza virus that relies on hemagglutinin, the glycoprotein that allows the influenza virus to attach to target cells, in this case cells in the human respiratory pathway.

Key Terms

- **endosome**: An endocytic vacuole through which molecules are internalized during endocytosis pass, en route to lysosomes.
- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **sialic**: Of or pertaining to sialic acid or its derivatives.

One of the best understood examples of virus entry into the host cell is the influenza viral infection. The glycoprotein responsible for attachment on the surface of an influenza viral particle is hemagglutinin (HA). HA is an antigenic glycoprotein. It is responsible for binding the virus to the cell that is being infected. HA proteins bind to cells with sialic acid on the membranes, such as cells in the upper respiratory tract or erythrocytes.

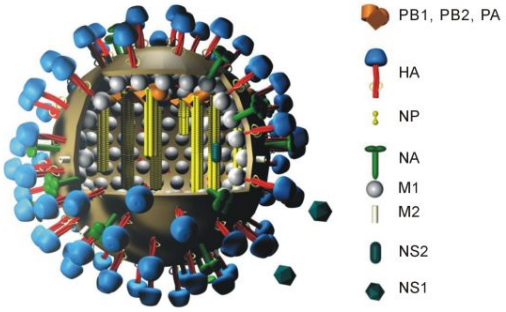

Figure: **Swine influenza**: A depiction of the different structures present on and in an influenza virus. Of special note is HA (hemagglutinin), the glycoprotein critical for influenza attachment and entry into host cells.

HA has two functions. First, it allows the recognition of target vertebrate cells, accomplished through the binding of these cells' sialic acid-containing receptors. Second, once bound, it facilitates the entry of the viral genome into the target cells by causing the fusion of the host endosomal membrane with the viral membrane. HA binds to the monosaccharide sialic acid that is present on the surface of its target cells, which causes the viral particles to stick to the cell's surface. The cell membrane then engulfs the virus and the portion of the membrane that encloses it pinches off to form a new membrane-bound compartment within the cell called an endosome, which contains the engulfed virus. The cell then attempts to begin digesting the contents of the endosome by acidifying its interior and transforming it into a lysosome.

However, as soon as the pH within the endosome drops to about 6.0, the original folded structure of the HA molecule becomes unstable, causing it to partially unfold and release a very hydrophobic portion of its peptide chain that was previously hidden within the protein. This so-called "fusion peptide" acts like a molecular grappling hook by inserting itself into the endosomal membrane and locking on. Then, when the rest of the HA molecule refolds into a new structure (which is more stable at the lower pH), it "retracts the grappling hook" and pulls the endosomal membrane right up next to the virus particle's own membrane, causing the two to fuse together. Once this has happened, the contents of the virus, including its RNA genome, are free to pour out into the cell's cytoplasm.

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9.9C: Replicative Cycle of Influenza A

Learning Objectives

- Contrast the roles of hemagglutinin and neuraminidase throughout the major stages of the replicative cycle of influenza A virus

Influenza A follows the typical life cycle of most influenza viruses. The infection and replication is a multi-step process:

- Binding to and entering the cell
- Delivering the genome to a site where it can produce new copies of viral proteins and RNA
- Assembling these components into new viral particles
- Exiting the host cell

Influenza viruses bind through hemagglutinin onto sialic acid sugars on the surfaces of epithelial cells, typically in the nose, throat, and lungs of mammals, and the intestines of birds (Step 1 in infection figure). After the hemagglutinin is cleaved by a protease, the cell imports the virus by endocytosis.

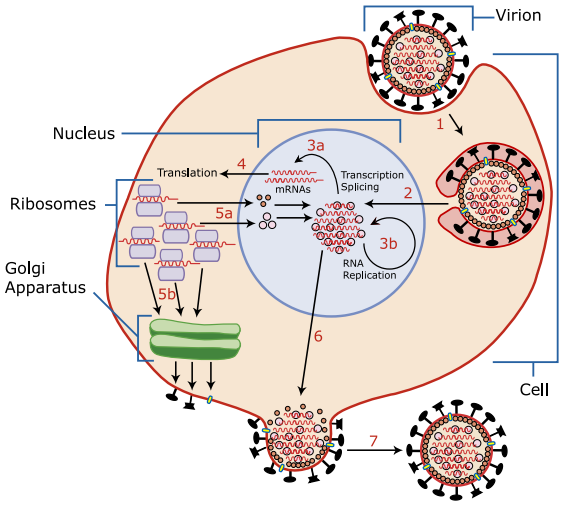

Figure: ***Influenza replication cycle****: Host invasion and replication cycle of an influenza virus. Step 1: Binding Step 2: Entry Step 3: Complex formation and transcription Step 4: Translation Step 5: Secretion Step 6: Assembly Step 7: Release*

The intracellular details are still being worked out. It is known that virions converge to the microtubule organizing center, interact with acidic endosomes, and finally enter the target endosomes for genome release. Once inside the cell, the acidic conditions in the endosome cause two events to happen:

1. The hemagglutinin protein fuses the viral envelope with the vacuole's membrane.
2. The M2 ion channel allows protons to move through the viral envelope and acidify the core of the virus, which causes the core to dissemble and release the viral RNA and core proteins.

The viral RNA (vRNA) molecules, accessory proteins, and RNA-dependent RNA polymerase are then released into the cytoplasm (Step 2 in figure). These core proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense vRNA (Steps 3a and b in figure).

The vRNA either enters into the cytoplasm and translated (Step 4) or remains in the nucleus. Newly synthesized viral proteins are either secreted through the Golgi apparatus onto the cell surface (in the case of neuraminidase and hemagglutinin, Step 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (Step 5a).

Other viral proteins have multiple actions in the host cell—including degrading cellular mRNA and using the released nucleotides for vRNA synthesis, and also inhibiting translation of host-cell mRNAs.

Negative-sense vRNAs that form the genomes of future viruses, RNA-dependent RNA polymerase, and other viral proteins are assembled into a virion. Hemagglutinin and neuraminidase molecules cluster into a bulge in the cell membrane. The vRNA and viral core proteins leave the nucleus and enter this membrane protrusion (Step 6). The mature virus buds off from the cell in a

sphere of the host phospholipid membrane, acquiring hemagglutinin and neuraminidase with this membrane coat (Step 7). As before, the viruses adhere to the cell through hemagglutinin; the mature viruses detach once their neuraminidase has cleaved sialic acid residues from the host cell. Drugs that inhibit neuraminidase, such as oseltamivir, therefore prevent the release of new infectious viruses and halt viral replication. After the release of new influenza viruses, the host cell dies.

Key Points

- A component of the viral coat, hemagglutinin, binds to the surface of target cells. After binding, the virus fuses and is imported by endocytosis.
- Once the vRNA is released into the cytoplasm, it is transported into the nucleus where it is transcribed. The resulting vRNAs are then transported into the cytoplasm and new viral particles are made.
- The endosome ‘s acidic environment breaks down the viron coat, releasing the vRNA. The acidic environment also promotes the release of the vRNA to proteins that are bound to it.
- Once new viral particles are made in the host cell and bud off, the host cell dies.

Key Terms

- **neuraminidase**: An antigenic enzyme, found on the surfaces of viruses, that catalyzes the hydrolysis of terminal acylneuraminic residues from oligosaccharides, glycoproteins, and glycolipids.
- **hemagglutinin**: An antigenic glycoprotein that causes agglutination of red blood cells.
- **sialic**: Of or pertaining to sialic acid or its derivatives.

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SECTION OVERVIEW

9. 10: Retroviruses: Double-Stranded RNA Viruses

Topic hierarchy

9.10A: Double-Stranded RNA Viruses - Retroviruses

9.10B: HIV Attachment and Host Cell Entry

9.10C: Retroviral RNA Genome

9.10D: Replicative Cycle of HIV

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