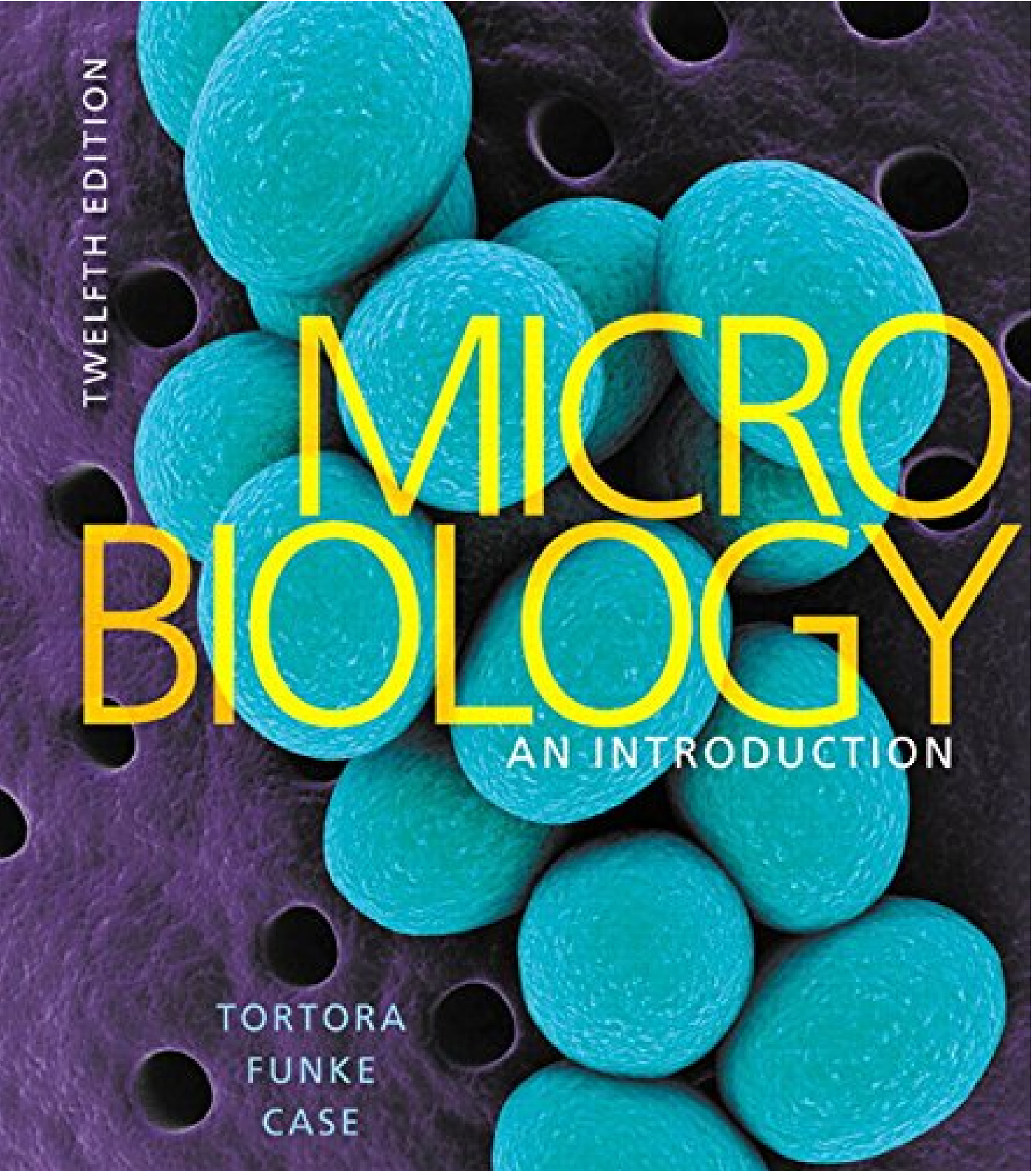

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ASM Recommended Curriculum Guidelines for Undergraduate Microbiology

The American Society for Microbiology (ASM) endorses a concept-based curriculum for introductory microbiology, emphasizing skills and concepts that remain important long after students exit the course. The ASM *Curriculum Guidelines for Undergraduate Microbiology Education* provide a framework for key microbiological topics and agree with scientific literacy reports from the American Association for the Advancement of Science and Howard Hughes Medical Institute. This textbook references part one of curriculum guidelines throughout chapters. When a discussion touches on one of the concepts, readers will see the ASM icon, along with a summary of the relevant statement.



ASM GUIDELINE CONCEPTS AND STATEMENTS

Evolution:

- Cells, organelles (e.g., mitochondria and chloroplasts), and all major metabolic pathways evolved from early prokaryotic cells.
- Mutations and horizontal gene transfer, with the immense variety of microenvironments, have selected for a huge diversity of microorganisms.
- Human impact on the environment influences the evolution of microorganisms (e.g., emerging diseases and the selection of antibiotic resistance).
- Traditional concept of species is not readily applicable to microbes due to asexual reproduction and the frequent occurrence of horizontal gene transfer.
- Evolutionary relatedness of organisms is best reflected in phylogenetic trees.

Cell Structure and Function:

- Structure and function of microorganisms have been revealed by the use of microscopy (including brightfield, phase contrast, fluorescent, and electron).
- Bacteria have unique cell structures that can be targets for antibiotics, immunity, and phage infection.
- Bacteria and Archaea have specialized structures (e.g. flagella, endospores, and pili) that often confer critical capabilities.
- While microscopic eukaryotes (for example, fungi, protozoa, and algae) carry out some of the same processes as bacteria, many of the cellular properties are fundamentally different.
- Replication cycles of viruses (lytic and lysogenic) differ among viruses and are determined by their unique structures and genomes.

Metabolic Pathways:

- Bacteria and Archaea exhibit extensive, and often unique, metabolic diversity (e.g. nitrogen fixation, methane production, anoxygenic photosynthesis).
- Interactions of microorganisms among themselves and with their environment are determined by their metabolic abilities (e.g., quorum sensing, oxygen consumption, nitrogen transformations).
- Survival and growth of any microorganism in a given environment depends on its metabolic characteristics.
- Growth of microorganisms can be controlled by physical, chemical, mechanical, or biological means.

Information Flow and Genetics:

- Genetic variations can impact microbial functions (e.g. in biofilm formation, pathogenicity, and drug resistance).
- Although the central dogma is universal in all cells, the processes of replication, transcription, and translation differ in Bacteria, Archaea, and Eukaryotes.
- Regulation of gene expression is influenced by external and internal molecular cues and/or signals.
- Synthesis of viral genetic material and proteins is dependent on host cells.
- Cell genomes can be manipulated to alter cell function.

Microbial Systems:

- Microorganisms are ubiquitous and live in diverse and dynamic ecosystems.
- Most bacteria in nature live in biofilm communities.
- Microorganisms and their environment interact with and modify each other.
- Microorganisms, cellular and viral, can interact with both human and nonhuman hosts in beneficial, neutral, or detrimental ways.

Impact of Microorganisms:

- Microbes are essential for life as we know it and the processes that support life (e.g., in biogeochemical cycles and plant and/or animal microbiota).
- Microorganisms provide essential models that give us fundamental knowledge about life processes.
- Humans utilize and harness microorganisms and their products.
- Because the true diversity of microbial life is largely unknown, its effects and potential benefits have not been fully explored.



In the Clinic

As a perinatal nurse, you must discuss the results of parvovirus B19 antibody testing with your 22-year-old patient. The patient is pregnant and has a high parvovirus IgM titer. **What does the high IgM titer indicate? What if she has high IgG and low IgM titers?**

Hint: Read about immunoglobulin classes on pages 473–475. Parvovirus B19 infection is discussed on page 595.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

17 Adaptive Immunity: Specific Defenses of the Host

Unlike innate immunity, adaptive immunity is induced and specific to a particular microbial invader or foreign substance. Adaptive immunity consists of two parts: humoral immunity and cellular immunity. In further contrast to innate immunity, adaptive immunity also includes a memory component.

Humoral immunity involves antibodies produced by B cells, whereas cellular immunity involves T cells. Both parts of adaptive immunity involve the recognition of specific antigens, followed by activation and clonal expansion of the immune cells, and result in the production of effector and memory cells. Effector cells in humoral immunity target antigens outside cells, such as bacteria replicating in the extracellular spaces of the host. Effector cells in cellular immunity, by contrast, target antigens inside the cells, for example, a virus-infected cell.

The phagocyte shown in the micrograph is important in both innate and adaptive immunity. Note the numerous cell membrane processes. These constantly extend and contract, which allows the B cell to move to and engulf bacteria.

See pages 440–441 for a Big Picture overview of the whole immune system.

Macrophages engulf bacteria and debris with their pseudopods. They digest the bacteria for their food.

The Adaptive Immune System

LEARNING OBJECTIVE

17-1 Compare and contrast adaptive and innate immunity.

Adaptive immunity is a range of microbial defenses that target specific pathogens. Unlike innate defenses, the adaptive immune system defenses are acquired through infection or vaccination and are highly specific. It was recognized long ago that immunity to certain infectious diseases can be acquired during an individual's life. If someone recovered from smallpox or measles, that person was almost always immune to that particular disease when exposed to it again. In some way, the body had acquired a memory of the infection that allowed it to adapt, to effectively curb infections from repeated exposures. Eventually, as medicine developed over the centuries, methods were found to mimic the adaptive immunity to disease by deliberately exposing people to harmless versions of pathogens that caused certain diseases, thus rendering them immune. We now call this *immunization* or *vaccination* (see Chapter 18, pages 493–500). Vaccination against smallpox, the first disease for which vaccination was developed, actually predated by nearly a hundred years any knowledge of microscopic pathogens.

The adaptive immune system comes into play only when the innate defenses—physical barriers such as skin and mucous membranes, phagocytic cells such as macrophages in the blood, and inflammation—fail to stop a microbe. While the innate system responses are the same regardless of the foreign substance, the adaptive system tailors its fight to the specific microbial pathogen, toxin, or other substance at hand. The defenses of the adaptive system take several days or more to fully develop, whereas the effects of the innate system responses are more immediate.

The first time the adaptive immune system meets and combats a particular foreign substance is called the *primary response.* Later interactions with that same cell or substance will cause a *secondary response,* which will be faster and more effective as a result of a "memory" of the first infection. This memory component is important and exclusive to the adaptive immune system. It also explains why someone who contracts and recovers from smallpox or measles can acquire a long-term immunity against those particular diseases.

Another important element of the adaptive immune system is its ability to differentiate between normal "self" cells and "nonself." This is essential, because without this ability the immune system might attack components of the body it is designed to protect. MM **Animation** Host Defenses: The Big Picture

CHECK YOUR UNDERSTANDING

Is vaccination an example of innate or adaptive immunity? **17-1**

Dual Nature of the Adaptive Immune System

LEARNING OBJECTIVE

17-2 Differentiate humoral from cellular immunity.

Adaptive immunity is considered a **dual system,** with humoral and cellular components. Next, we will briefly summarize both humoral and cellular immunity.

Overview of Humoral Immunity

From ancient times until well into the nineteenth century, the medical community believed that health depended on four different body fluids, or *humors*—blood, phlegm, black bile, and yellow bile. The new science of immunology adopted the term **humoral immunity** when describing immunity brought about by protective molecules called **antibodies.** Antibodies combat foreign molecules that we refer to as **antigens.** Humoral immunity involves **B lymphocytes,** more commonly known as **B cells,** which remove viruses, bacteria, and toxins from body tissue fluids and blood by recognizing antigens and making antibodies against them. The recognition of different antigens depends on *B cell receptors* for antigens that coat the surface of the B cell.

B cells were named for their source when they were first observed, the *bursa of Fabricius,* which is a specialized organ of birds. In humans, lymphocytes are initially produced in the fetal liver, but by about the third month of life, the site of the creation and maturation, or schooling, of the B cells becomes the red bone marrow.

Clinical Case: It's Just a Scratch

JoAnna Marsden is a medical examiner at a large city hospital. She receives an autopsy order for Mrs. Vasquez, a 44-year-old woman who recently died after an emergency department visit. According to the medical file, Mrs. Vasquez went to the emergency department complaining of "not feeling well" for several days. Initial examination by the physician revealed a scratch on Mrs. Vasquez's right forearm, but there was no sign of infection. Mrs. Vasquez was treated with oxygen but became progressively worse. She died 4 hours after admission. When Dr. Marsden performs the autopsy on Mrs. Vasquez, she finds that Mrs. Vasquez has died from disseminated intravascular coagulation consistent with septic shock.

What caused Mrs. Vasquez to die from disseminated intravascular coagulation and septic shock? Read on to find out.

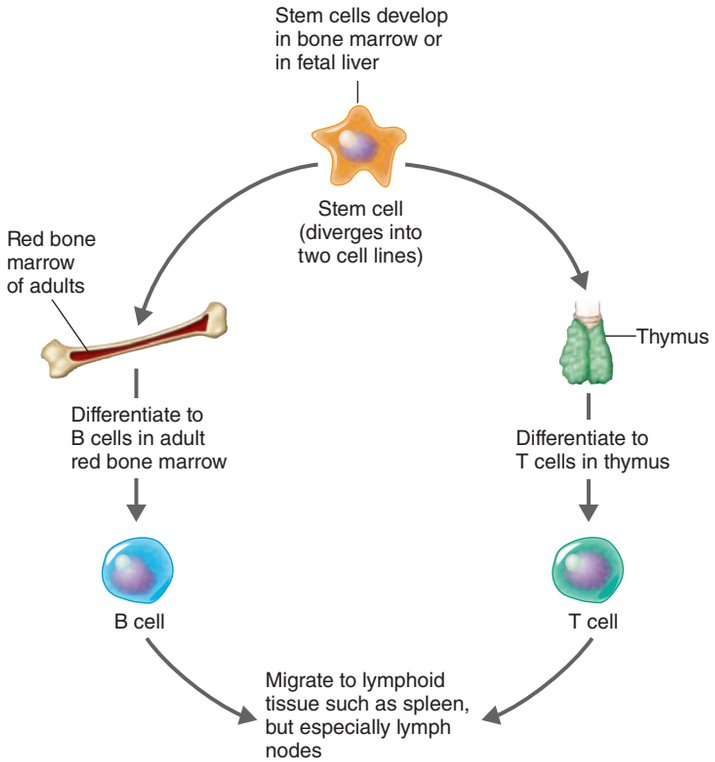


Figure 17.1 Differentiation of T cells and B cells. Both B cells and T cells originate from stem cells in adult red bone marrow or in the fetal liver. Some cells pass through the thymus and emerge as mature T cells. Other cells probably remain in the red bone marrow and become B cells. Both types of cells then migrate to lymphoid tissues, such as the lymph nodes or spleen.

Q Which cells, T or B, make antibodies?

Overview of Cellular Immunity

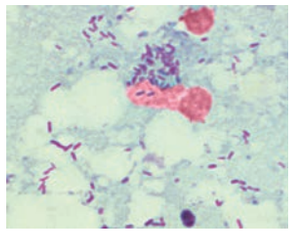
T lymphocytes, or **T cells,** are the basis of **cellular immunity.** This form of immunity is also called **cell-mediated immunity.** T cells do not bind to antigens directly, but recognize antigenic peptides after they have been processed by phagocytic cells such as macrophages.

T cells and B cells both develop from stem cells in the bone marrow, as Figure 17.1 illustrates. However, T cells owe their name to the fact that unlike B cells, they mature under the influence of the *thymus.*

Both T cells and B cells are found primarily in blood and lymphoid organs. The responses of cellular immunity center on attacking antigens that make their way inside cells, whereas humoral immunity responses are directed at antigens that are extracellular (such as in blood or other body fluids). This means that cellular immunity is generally best at fighting viruses that have infected a cell, as well as some fungal and parasitic infections, which generally involve pathogens much larger than bacteria and viruses. Because humoral immunity fights invaders outside cells, its efforts tend to focus on bacteria and their toxins, as well as viruses before they penetrate the target cells.

Clinical Case

Dr. Marsden performs a Gram stain on a blood smear from the patient (see the figure). She needs to know what bacteria, if any, caused Mrs. Vasquez's disseminated intravascular coagulation, septic shock, and subsequent death.



Describe the bacteria in the figure. What other cells can you identify?

469 470 474 477 481 484

T cells (like B cells) respond to antigens by means of receptors on their surface—**T cell receptors (TCRs).** Contact with an antigen complementary to a TCR can cause certain types of T cells to proliferate and secrete *cytokines* rather than antibodies. Next, we will discuss these chemical messengers that instruct other cells to perform certain functions.

CHECK YOUR UNDERSTANDING

What type of cell is most associated with humoral immunity, and what type of cell is the basis of cellular immunity? 17-2

Cytokines: Chemical Messengers of Immune Cells

LEARNING OBJECTIVE

17-3 Identify at least one function of each of the following: cytokines, interleukins, chemokines, interferons, TNF, and hematopoietic cytokines.

The immune response requires complex interactions between different cells. The communication required for this is mediated by chemical messengers called **cytokines.** These are soluble proteins or glycoproteins that are produced by practically all cells of the immune system in response to a stimulus. Many cytokines—there are probably more than 200—have common names that reflect their functions known at the time of the discovery; some are now known to have multiple functions. A cytokine acts only on a cell that has a receptor for it.

Cytokines that serve as communicators between leukocytes are now known as **interleukins** (between leukocytes). The role of cytokines in stimulating the immune system has suggested

Interleukin-12: The Next "Magic Bullet"?

Worldwide, HIV/AIDS-related illnesses kill 1.7 million people, and measles kills about 160,000 people annually. If laboratory tests are any indication of the future, the cytokine IL-12 (interleukin-12) could be the "magic bullet" against AIDS, cancer, and a host of other diseases.

IL-12 inhibits the humoral response and activates T_H1 cellular immunity. Scientists at the National Institute of Allergy and Infectious Diseases (NIAID) have found that treating mice with IL-12 can help activate phagocytes to kill *Cryptosporidium hominis* and *Toxoplasma gondii* protozoa, as well as *Mycobacterium avium;* these are common opportunistic infections in people with late-stage AIDS.

Researchers have shown that HIV and measles virus decrease the production of IL-12, which may make the patient more susceptible to secondary infections. When treated with IL-12, however, T_H cells taken from HIV-positive people responded to viruses, including HIV.

Interleukin-12 is known to inhibit about 20 kinds of tumors in mice by stimulating white blood cells to kill tumor cells. NIAID has begun a clinical trial to test the effectiveness of IL-12 in patients with breast cancer.

IL-12 activates the T_H1 pathway, resulting in activation of cellular immunity, macrophages, and promotion of phagocytosis through opsonization and inflammation. This can cause the symptoms associated with chronic inflammatory diseases, including Crohn's disease, psoriasis, rheumatoid arthritis, and multiple sclerosis. NIAID researchers developed the concept of blocking IL-12 with monoclonal antibodies that bind secreted IL-12. Psoriasis patients showed dramatic improvements after treatment with IL-12 monoclonal antibodies (ustekinumab) compared to the placebo-treated patients.

Will IL-12 be a panacea? Further studies are needed to determine whether treatment with IL-12 could have adverse effects, such as autoimmune disease, or whether blocking IL-12 could allow growth of cancer cells.

their use as therapeutic agents (see the Applications of Microbiology box above).

A family of small cytokines that induces the migration of leukocytes into areas of infection or tissue damage is called **chemokines,** from *chemotaxis.* These are especially important for infections by HIV (see Chapter 19, page 536).

Another family of cytokines is the **interferons (IFNs)** (see Chapter 16) which were originally named for one of their functions: interfering with viral infections in host cells. A number of antiviral interferons are available as commercial products in treating disease conditions such as hepatitis and some cancers. INFγ stimulates the immune system.

A very important cytokine family is the **tumor necrosis factor (TNF),** which was originally named because tumor cells were observed to be one of its targets. These cytokines are a strong factor in inflammatory reactions of autoimmune diseases such as rheumatoid arthritis. Monoclonal antibodies (see pages 501–503) that block the action of TNF are an available therapy for some of these conditions.

Another family of cytokines, **hematopoietic cytokines,** function in controlling the pathways by which stem cells develop into different red or white blood cells (see page 446). Some of these are interleukins, with designations such as IL-1; others are termed *colony stimulating factors (CSF).* An example is granulocyte colony stimulating factor (G-CSF). This particular CSF stimulates the production of neutrophils from the granulocyte monocyte precursors. Another, GM-CSF, is used therapeutically to increase the numbers of protective macrophages and granulocytes in patients undergoing red bone marrow transplants.

Cytokines, among other things, may stimulate cells to produce more cytokines. This feedback loop occasionally gets out of control, resulting in a harmful overproduction of cytokines—a **cytokine storm.** This can do significant damage to tissues, which appears to be a factor in the pathology of certain diseases and conditions such as influenza, Ebola hemorrhagic fever, graft-versus-host disease (page 531), and sepsis. Also, see the discussion of superantigens on page 427.

CHECK YOUR UNDERSTANDING

What is the function of cytokines? **17-3**

Antigens and Antibodies

LEARNING OBJECTIVES

17-4 Define *antigen, epitope,* and *hapten*.

17-5 Explain antibody function, and describe the structural and chemical characteristics of antibodies.

17-6 Name one function for each of the five classes of antibodies.

Antigens

Substances that cause the production of antibodies are called **antigens**—from *anti*body *gen*erators. Most antigens are either proteins or large polysaccharides. Lipids and nucleic acids are usually antigenic only when combined with proteins and polysaccharides. Antigenic compounds are often components of invading microbes, such as capsules, cell walls, flagella, fimbriae, and toxins of bacteria; the coats of viruses; or the surfaces of other types of microbes. Nonmicrobial antigens include pollen, egg white, blood cell surface molecules, serum proteins from other individuals or species, and surface molecules of transplanted tissues and organs.

Antigens play key roles in the response of the immune system. Antigens provoke a highly specific immune response that,

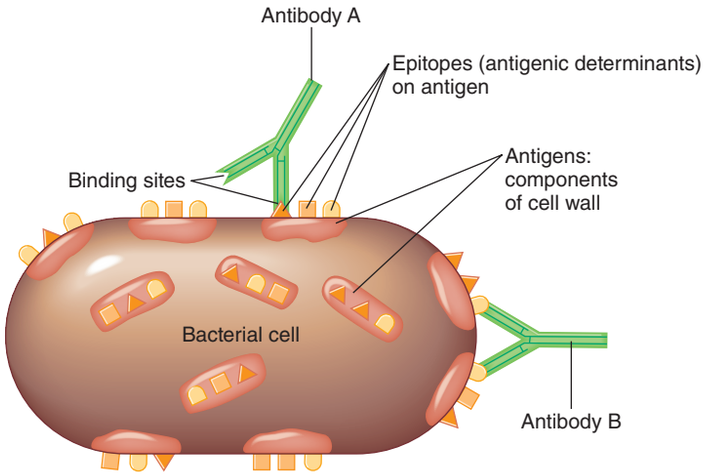


Figure 17.2 Epitopes (antigenic determinants). In this illustration, the epitopes are components of the antigen—the bacterial cell wall. Each antigen carries more than one epitope. Each Y-shaped antibody molecule has two binding sites that can attach to a specific epitope on an antigen. An antibody can also bind to identical epitopes on two different cells at the same time, which can cause neighboring cells to aggregate.

Q Which would have more epitopes: a protein or a lipid? Why?

in humoral immunity, results in the production of antibodies that are capable of recognizing the antigen that gave rise to them. Antigens that cause such a response are, therefore, often more descriptively known as *immunogens*.

Generally, antibodies recognize and interact with specific regions on antigens called **epitopes** or **antigenic determinants** (Figure 17.2). The nature of this interaction depends on the size, shape, and chemical structure of the binding site on the antibody molecule.

Pathogenic bacteria characteristically possess a number of recognizable antigens called pathogen-associated molecular patterns (PAMPs, discussed on page 442). PAMPs serve as warning flags of an invading organism that the host can recognize by means of receptors. The best-known of these receptors is the extended family of Toll-like receptors (TLRs).*

Most antigens have a molecular weight of 10,000 or higher. A foreign substance that has a low molecular weight is often not antigenic unless it is attached to a carrier molecule. These low-molecular-weight compounds are called **haptens** (Figure 17.3). Once an antibody against the hapten has been formed, the antibody will react with the hapten independent of the carrier molecule. Penicillin is a good example of a hapten. This drug is not antigenic by itself, but some people develop an allergic reaction to it. (Allergic reactions are a type of immune response.) In these people, when penicillin combines with host proteins, the resulting combined molecule initiates an immune response.

*Fruit flies defend themselves from fungal infections by means of a protein called *Toll*—named for the German word for weird or strange. The term derives from the fact that the Toll protein also is involved in development of the fruit fly embryo and that flies without it have a strange, or weird, appearance.

Antibodies

Antibodies are globulin proteins, and we have come to use the term **immunoglobulins (Ig)** for antibodies. Globulin proteins are compact and relatively soluble. Antibodies are made in response to an antigen and can recognize and bind to the antigen. As shown in Figure 17.2, a bacterium or virus may have several epitopes that cause the production of different antibodies.

Antibody Structure

Each antibody has at least two identical antigen-binding sites that bind to epitopes. The number of antigen-binding sites on an antibody is called the **valence** of that antibody. For example, most human antibodies have two binding sites; therefore, they are bivalent.

Because a bivalent antibody has the simplest molecular structure, it is called a **monomer.** A typical antibody monomer has four protein chains: two identical *light chains* and two identical *heavy chains.* ("Light" and "heavy" refer to the relative molecular weights.) The chains are joined by disulfide links and other bonds to form a Y-shaped molecule. The Y-shaped molecule is flexible and can assume a T shape (notice the hinge region in Figure 17.4a).

The two sections located at the ends of the Y arms are called *variable (V) regions.* These bind to the epitopes (Figure 17.4b). The amino acid sequences and, therefore, the three-dimensional structure of these two variable regions are identical on any one antibody. Their structure makes the two antigen-binding sites found on each antibody monomer. The stem of the antibody monomer and the lower parts of the arms of the Y are called the *constant (C) regions.* They are the same for a particular class of immunoglobulin. There are five major types of C regions, which account for the five major classes of immunoglobulins (described shortly).

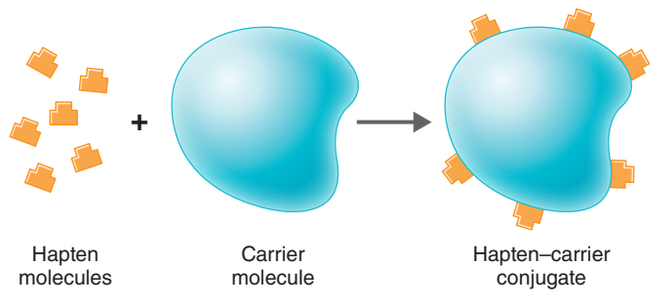
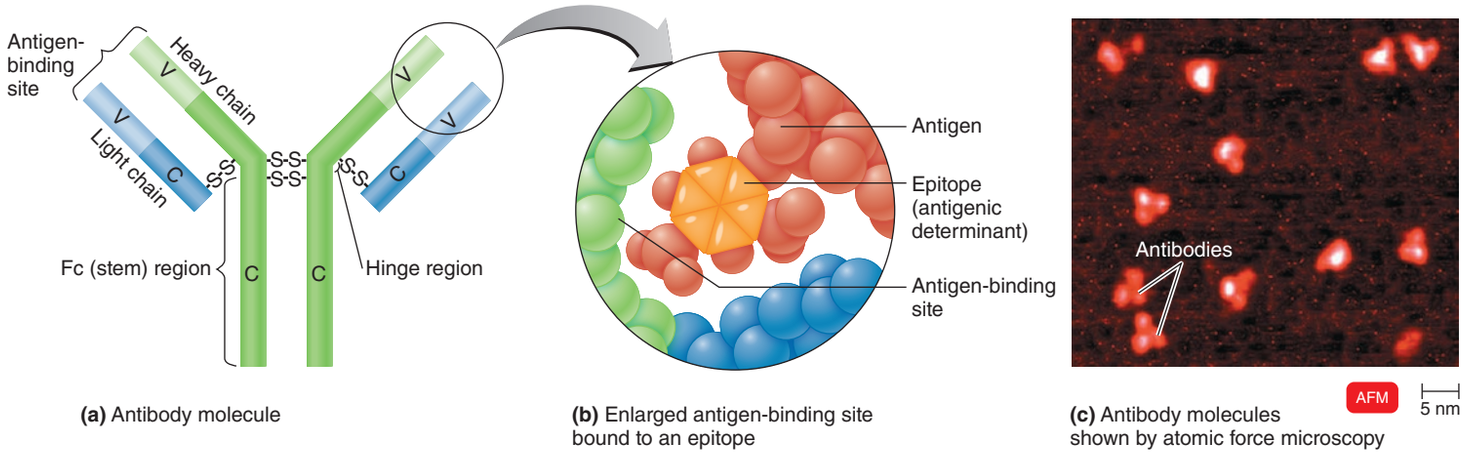


Figure 17.3 Haptens. A hapten is a molecule too small to stimulate antibody formation by itself. However, when the hapten is combined with a larger carrier molecule, usually a serum protein, the hapten and its carrier together form a conjugate that can stimulate an immune response.

Q How does a hapten differ from an antigen?



(a) Antibody molecule

(b) Enlarged antigen-binding site bound to an epitope

(c) Antibody molecules shown by atomic force microscopy

Figure 17.4 The structure of a typical antibody molecule. The Y-shaped molecule is composed of two light chains and two heavy chains linked by disulfide bridges (S—S). Most of the molecule is made up of constant regions (C), which are the same for all antibodies of the same class. The amino acid sequences of the variable regions (V), which form the two antigen-binding sites, differ from antibody to antibody.

Q What is responsible for the specificity of each different antibody?

The stem of the Y-shaped antibody monomer is called the *Fc region,* so named because when antibody structure was first being identified, it was a fragment (F) that crystallized (c) in cold storage.

These Fc regions are often important in immunological reactions. If left exposed after both antigen-binding sites attach to an antigen such as a bacterium, the Fc regions of adjacent antibodies can bind complement. This leads to the destruction of the bacterium (see Figure 16.12, page 459). Conversely, the Fc region may bind to a cell, leaving the antigen-binding sites of adjacent antibodies free to react with antigens.

Immunoglobulin Classes

The simplest and most abundant immunoglobulins are monomers, but they can also assume some differences in size and arrangement. The five classes of Igs are designated IgG, IgM, IgA, IgD, and IgE. Each class has a different role in the immune response. The structures of IgG, IgD, and IgE molecules are Y-shaped. Molecules of IgA and IgM are aggregates of two or five monomers, respectively, that are joined together. The structures and characteristics of the immunoglobulin classes are summarized in **Table 17.1**.

IgG The name **IgG** is derived from the blood fraction gamma globulin. IgG accounts for about 80% of all antibodies in serum. In regions of inflammation, these monomer antibodies readily cross the walls of blood vessels and enter tissue fluids. Maternal IgG antibodies, for example, can cross the placenta and confer passive immunity to a fetus. IgG antibodies protect against circulating bacteria and viruses, neutralize bacterial toxins, trigger the complement system, and, when bound to antigens, enhance the effectiveness of phagocytic cells.

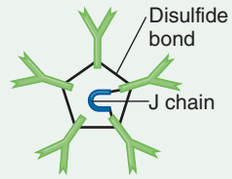
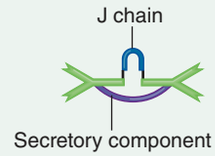
IgM Antibodies of the **IgM** class (the M refers to *macro,* reflecting their large size) make up 6% of the antibodies in serum. IgM has a pentamer structure consisting of five monomers held together by a polypeptide called a *joining (J) chain*. The large size of the molecule prevents IgM from moving about as freely as IgG does, so IgM antibodies generally remain in blood vessels without entering the surrounding tissues.

IgM is the predominant type of antibody involved in the response to the ABO blood group antigens on the surface of red blood cells (see Table 19.2, page 522). It is much more effective than IgG in causing the clumping of cells and viruses (see the discussion of agglutination on pages 504–505) and in reactions involving the activation of complement (see Figure 16.10 on page 457).

The fact that IgM appears first in response to a primary infection and is relatively short-lived makes it uniquely valuable in diagnosing disease. If high concentrations of IgM against a pathogen are detected in a patient, it is likely that the disease observed is caused by that pathogen. The detection of IgG, which is relatively long-lived, may indicate only that immunity against a particular pathogen was acquired in the more distant past.

IgA **IgA** accounts for only about 13% of the antibodies in serum, but it is by far the most common form in mucous membranes and in body secretions such as mucus, saliva, tears, and breast milk. If we take this into consideration, IgA is the most abundant immunoglobulin in the body. The form of IgA that circulates in serum, *serum IgA,* is usually in the form of a monomer. The most effective form of IgA, however, consists of two connected monomers that form a *dimer* called *secretory IgA*. It is produced in this form by plasma cells in the mucous membranes—as much as 15 grams per day, mostly by intestinal

TABLE 17.1 A Summary of Immunoglobulin Classes

Characteristics	IgG	IgM	IgA	IgD	IgE
					
Structure	Monomer	Pentamer	Dimer (with secretory component)	Monomer	Monomer
Percentage of Total Serum Antibody	80%	6%	13%*	0.02%	0.002%
Location	Blood, lymph, intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears, saliva, mucus, intestine, milk), blood, lymph	B cell surface, blood, lymph	Bound to mast and basophil cells throughout body, blood
Molecular Weight	150,000	970,000	405,000	175,000	190,000
Half-Life in Serum	23 days	5 days	6 days	3 days	2 days
Complement Fixation	Yes	Yes	No†	No	No
Placental Transfer	Yes	No	No	No	No
Known Functions	Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn	Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection	Localized protection on mucosal surfaces	Serum function not known; presence on B cells functions in initiation of immune response	Allergic reactions; possibly lysis of parasitic worms

*Percentage in serum only; if mucous membranes and body secretions are included, percentage is much higher.
†May be yes via alternative pathway.

epithelial cells. Each dimer then enters and passes through a mucosal cell, where it acquires a polypeptide called a *secretory component* that protects it from enzymatic degradation. The main function of secretory IgA is probably to prevent the attachment of microbial pathogens to mucosal surfaces. This is especially important in resistance to intestinal and respiratory pathogens. Because IgA immunity is relatively short-lived, the length of immunity to many respiratory infections is correspondingly short. IgA's presence in a mother's milk, especially the colostrum, probably helps protect infants from gastrointestinal infections.

IgD **IgD** antibodies make up only about 0.02% of the total serum antibodies. Their structure resembles that of IgG molecules. IgD antibodies are found in blood, lymph, and particularly on the surfaces of B cells. Serum IgD has no well-defined function; on B cells it assists in the immune response.

IgE Antibodies of the **IgE** class are slightly larger than IgG molecules; they constitute only 0.002% of the total serum antibodies. IgE molecules bind tightly by their Fc (stem) regions to

Clinical Case

Gram-negative rods are visible inside white blood cells. Dr. Marsden identifies these particular gram-negative rods as *Capnocytophaga canimorsus* bacteria. This species is found in cats or dogs and can be transmitted to people through bites, licking, scratching, or other types of exposure to the animal. Dr. Marsden talks to Mr. Vasquez, who confirms that the scratch on his wife's arm was from the family dog. Dr. Marsden is puzzled, because most people who have contact with dogs do not develop *Capnocytophaga* infections.

What molecules normally made by B cells combat bacterial infections?

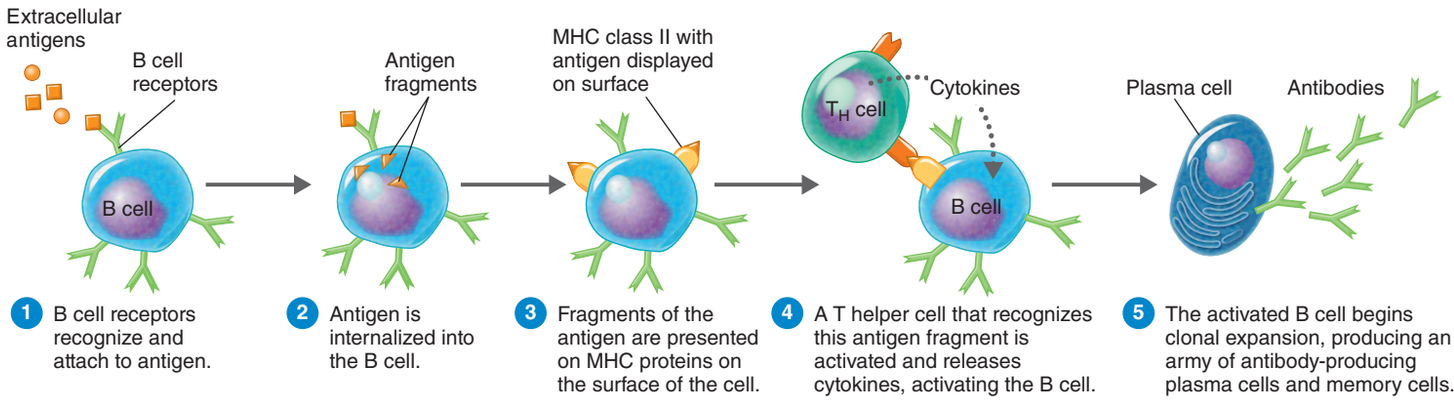


Figure 17.5 Activation of B cells to produce antibodies. In this illustration, the B cell is producing antibodies against a T-dependent antigen.

Q How does activation by T-independent antigens differ from this figure?

receptors on mast cells and basophils, specialized cells that participate in allergic reactions (see Chapter 19). When an antigen such as pollen links with the IgE antibodies attached to a mast cell or basophil (see Figure 19.1a, page 517), that cell releases histamine and other chemical mediators. These chemicals provoke a response—for example, an allergic reaction such as hay fever. However, the response can be protective as well, for it attracts complement and phagocytic cells. This is especially useful when the antibodies bind to parasitic worms. The concentration of IgE is greatly increased during some allergic reactions and parasitic infections, which is often diagnostically useful.

CHECK YOUR UNDERSTANDING

- Does an antibody react with a bacterium as an antigen or as an epitope? **17-4**
- The original theoretical concepts of an antibody called for a rod with antigenic determinants at each end. What is the primary advantage of the Y-shaped structure that eventually emerged? **17-5**
- Which class of antibody is most likely to protect you from a common cold? **17-6**

Humoral Immunity Response Process

LEARNING OBJECTIVES

17-7 Compare and contrast T-dependent and T-independent antigens.

17-8 Differentiate plasma cell from memory cell.

17-9 Describe clonal selection.

17-10 Describe how a human can produce different antibodies.

As we have seen, the humoral (antibody-mediated) response is carried out by antibodies. Antibodies are produced by a special group of lymphocytes called B cells. The process that leads to the production of antibodies starts when B cells are exposed to *free,* or *extracellular, antigens.*

Clonal Selection of Antibody-Producing Cells

Each B cell carries immunoglobulins on its surface that are part of its makeup. The majority of the B cell's surface immunoglobulins are IgM and IgD—all of which are specific for the recognition of the same epitope. Ten percent or fewer of B cells carry other classes of immunoglobulins, but in certain locations their numbers may be high. For example, B cells in the intestinal mucosa are rich in IgA. B cells may carry at least 100,000 identical immunoglobulin molecules embedded in their surface membranes.

When a B cell's immunoglobulins bind to the epitope for which they become specific, the B cell is *activated.* An activated B cell undergoes **clonal expansion,** or proliferation. B cells usually require the assistance of a **T helper cell (T_H)** as shown in **Figure 17.5**. (T cells will be the subject of a detailed discussion later in this chapter.) An antigen that requires a T_H cell for antibody production is known as a **T-dependent antigen.** T-dependent antigens are mainly proteins, such as those found on viruses, bacteria, foreign red blood cells, and haptens with their carrier molecules.

For antibodies to be produced in response to a T-dependent antigen, it is necessary that both B and T cells be activated and interact. The process is initiated when the B cell contacts an antigen. It is important to note that the antigen contacts the surface immunoglobulins on the B cell and is enzymatically processed within the B cell and that fragments of it are combined with the **major histocompatibility complex (MHC).** The MHC is a collection of genes that encode molecules of genetically diverse glycoproteins (that is, part carbohydrate and part protein). Class I MHC are found on the plasma membranes of mammalian nucleated cells. They identify "self," preventing the immune system from making antibodies that would be harmful to the host. Class II MHC molecules exist only on the surface of antigen-presenting molecules (APCs)—including B cells.

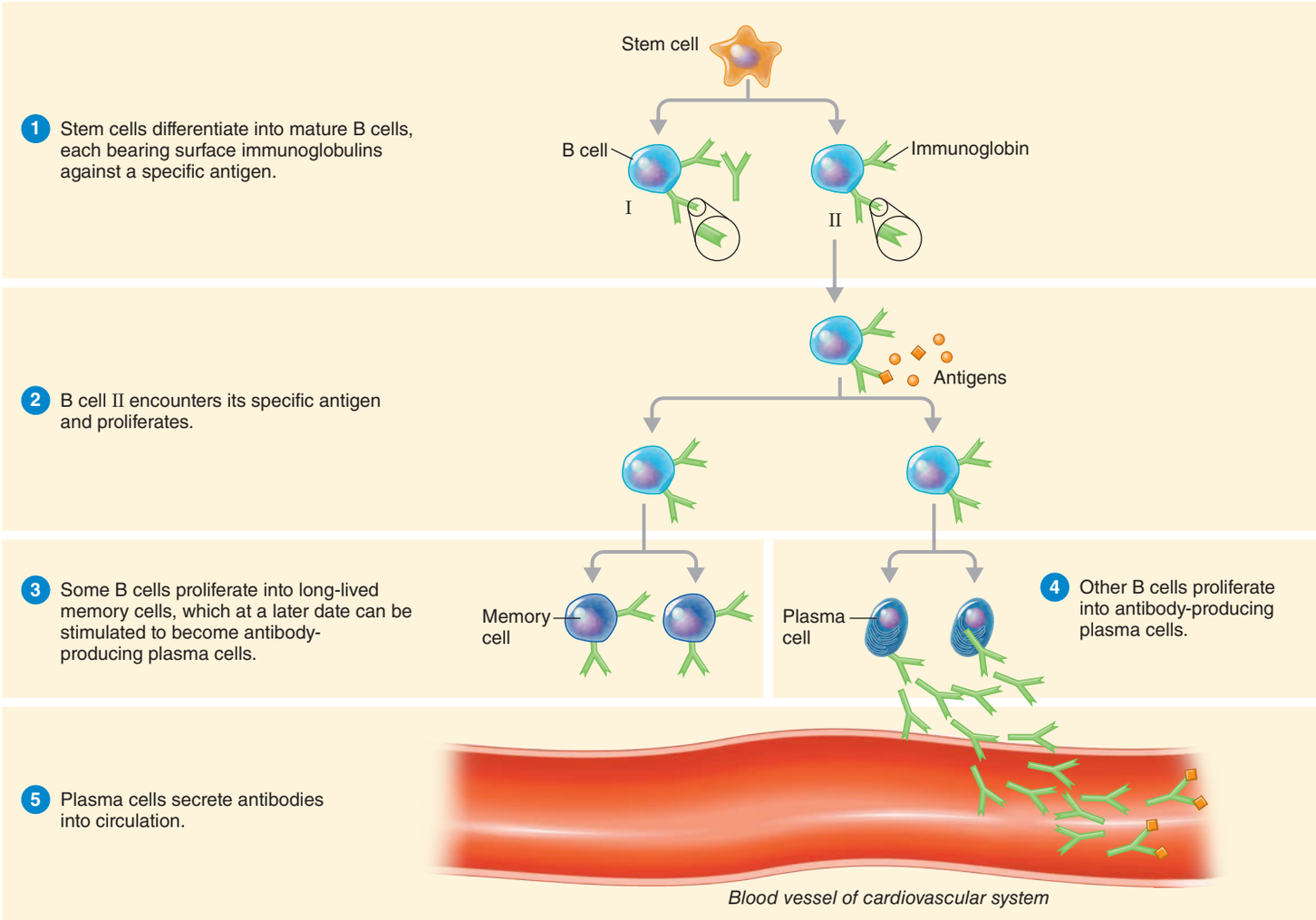


Figure 17.6 Clonal selection and differentiation of B cells. B cells can recognize an almost infinite number of antigens, but each particular cell recognizes only one type of antigen. An encounter with a particular antigen triggers the proliferation of a cell that is specific for that antigen (here, B cell "II") into a clone of cells with the same specificity, hence the term *clonal selection*. The initial antibodies produced are generally IgM, but later the same cell might produce different classes of antibody, such as IgG or IgE; this is called *class switching*.

Q What caused cell "II" to respond?

When an inactive B cell meets an antigen that can bind to its particular surface receptor, it will engulf and process it, displaying antigen fragments bound to its MHC class II molecules. This, in turn, attracts T helper cells to the B cells. As shown in Figure 17.5 step 3, the T helper cell in contact with the antigenic fragment presented on the surface of the B cell begins producing cytokines that activate the B cell. The B cell proliferates into a large clone of cells. Some of these cells differentiate into antibody-producing plasma cells. Other clones become long-lived memory cells that are responsible for the enhanced secondary response to an antigen. This process of clonal selection is shown in Figure 17.6.

As mentioned earlier, IgM is the first antibody B cells make during the primary response to an antigen. But an individual B cell is also capable of making different classes of antibody, such as IgG, IgE, or IgA, all with unchanged antigenic specificity. Termed **class switching,** this is observed, especially, in the case of the primary and secondary immune response (see Figure 17.17). Generally speaking, when IgG begins to be produced in the secondary response, the production of IgM will decrease or be sharply curtailed.

The pool of B cells does not contain many that are harmfully reactive against host tissue, or self. These are usually eliminated at the immature lymphocyte stage by the process of **clonal deletion.**

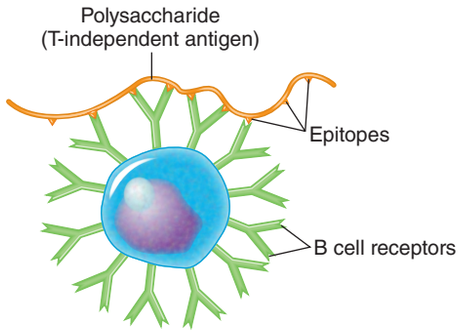


Figure 17.7 T-independent antigens. T-independent antigens have repeating units (epitopes) that can cross-link several antigen receptors on the same B cell. These antigens stimulate the B cell to make antibodies without the aid of T helper cells. The polysaccharides of bacterial capsules are examples of this type of antigen.

Q How can you differentiate T-dependent from T-independent antigens?

Antigens that stimulate B cells directly without the help of T cells are called **T-independent antigens.** Such antigens are characterized by repeating subunits such as are found in polysaccharides or lipopolysaccharides. Bacterial capsules are often good examples of T-independent antigens. The repeating subunits, as shown in **Figure 17.7**, can bind to multiple B cell receptors, which is probably why they do not require T cell assistance. T-independent antigens generally provoke a weaker immune response than do T-dependent antigens. This response is composed primarily of IgM, and no memory cells are generated. The immune system of infants may not be stimulated by T-independent antigens until about age 2. MM **Animations** Antigen Processing and Presentation: Overview; Humoral Immunity: Clonal Selection and Expansion

The Diversity of Antibodies

The human immune system is capable of recognizing a mind-boggling number of different antigens—an estimated minimum of 1 quadrillion antigens. The number of genes required for this amount of diversity would seem to require a major part of an individual's inherited DNA. But an adequate amount of antibody diversity is derived from a set of just hundreds of genes. Simplistically, the mechanism is analogous to the generation of huge numbers of words from a limited alphabet. This "alphabet" is found in the random rearrangements of the nucleotide sequence for the variable (V) region. These rearrangements occur even when no antigen is present during the early stages of the differentiation of a B cell. The details of this mechanism are quite complex, but the result is that only a relatively small amount of DNA is required to cope with the enormous number of different antigens that might be encountered. A different gene is not needed to respond to each antigen.

CHECK YOUR UNDERSTANDING

- Would pneumococcal pneumonia (see Figure 24.11, page 689) require a T_H cell to stimulate a B cell to form antibodies? **17-7**
- Plasma cells produce antibodies; do they also produce memory cells? **17-8**
- In what way does a B cell that encounters an antigen function as an antigen-presenting cell? **17-9**
- On what part of the antibody molecule do we find the amino acid sequence that makes the huge genetic diversity of antibody production possible? **17-10**

Antigen–Antibody Binding and Its Results

LEARNING OBJECTIVE

17-11 Describe four outcomes of an antigen–antibody reaction.

When an antibody encounters an antigen for which it is specific, an **antigen–antibody complex** rapidly forms. An antibody binds to an antigen, such as a bacterium, at a specific portion called the *epitope,* or *antigenic determinant*.

The strength of the bond between an antigen and an antibody is called **affinity.** In general, the closer the physical fit between antigen and antibody, the higher the affinity. Antibodies tend to recognize the shape of the antigen's epitope, giving the *specificity* to the antigen–antibody interaction. They can distinguish between minor differences in the amino acid sequence of a protein and even between two amino acid isomers (see Figure 2.13, page 40). Therefore, antibodies can be used to differentiate between the viruses of hepatitis B and hepatitis C and between bacteria of different strains, for example.

The binding of an antibody to an antigen protects the host by tagging foreign cells and molecules for destruction by phagocytes and complement. The antibody molecule itself is not damaging to the antigen. Foreign organisms and toxins are rendered harmless by only a few mechanisms, as summarized in **Figure 17.8**. These are agglutination, opsonization, neutralization, antibody-dependent cell-mediated cytotoxicity, and the activation of complement leading to opsonization, inflammation, and cell lysis (see Figure 16.12, page 459).

Clinical Case

Antibodies, especially IgM antibodies, are made in response to bacterial infections. In her research, Dr. Marsden learns that *Capnocytophaga* possesses T-independent antigens.

What steps are required for an antibody response to these antigens?

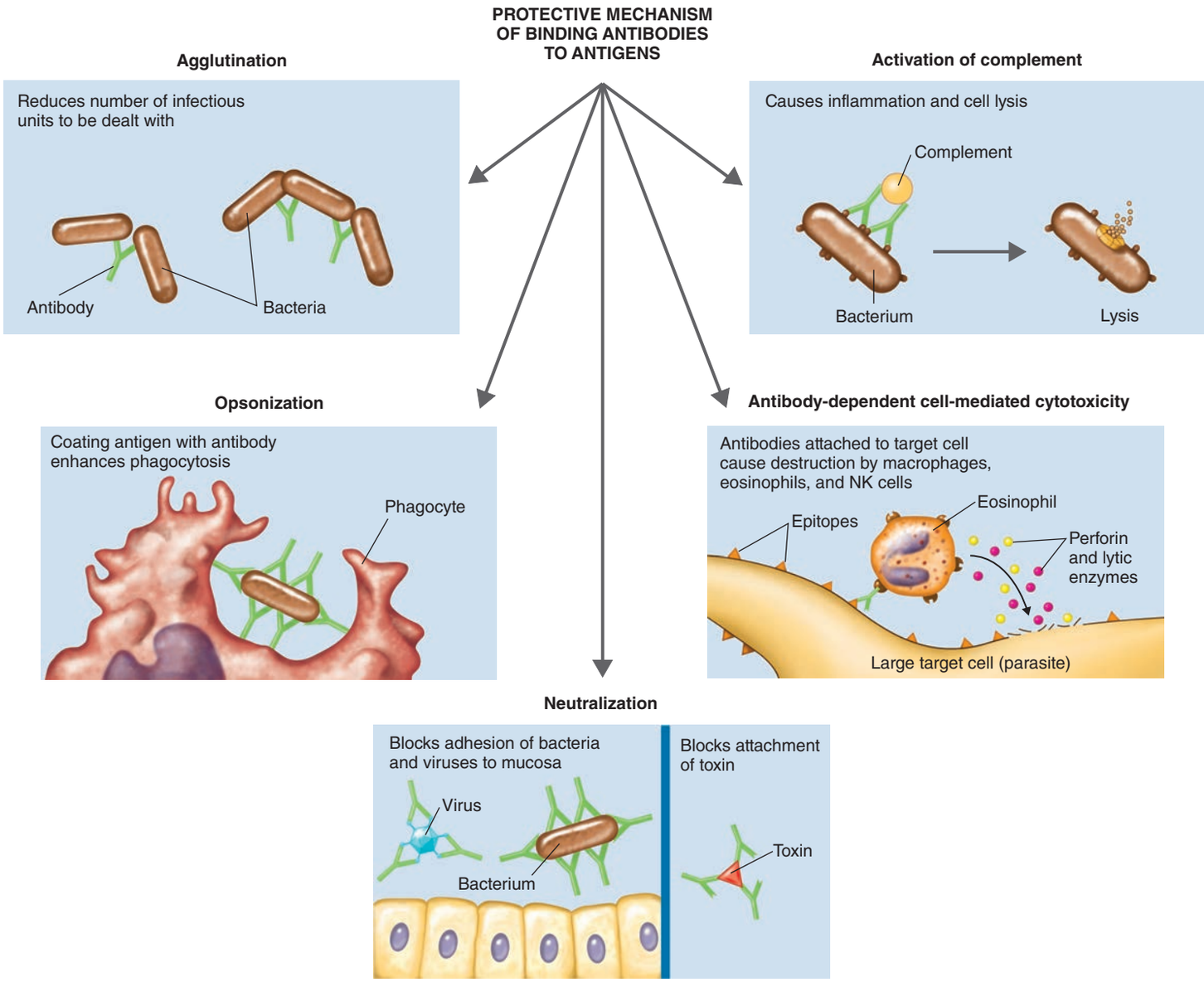


Figure 17.8 The results of antigen–antibody binding. The binding of antibodies to antigens to form antigen–antibody complexes tags foreign cells and molecules for destruction by phagocytes and complement.

Q What are some of the possible outcomes of an antigen–antibody reaction?

In **agglutination,** antibodies cause antigens to clump together. For example, the two antigen-binding sites of an IgG antibody can combine with epitopes on two different foreign cells, aggregating the cells into clumps that are more easily ingested by phagocytes. Because of its more numerous binding sites, IgM is more effective at cross-linking and aggregating particulate antigens (see Figure 18.5, page 504). IgG requires 100 to 1000 times as many molecules for the same results. (In Chapter 18, we will see how agglutination is important in the diagnosis of some diseases.)

For **opsonization,** the antigen, such as a bacterium, is coated with antibodies, or complement proteins, that enhance its ingestion and lysis by phagocytic cells. **Antibody-dependent cell-mediated cytotoxicity** (see pages 484–485 and Figure 17.16) resembles opsonization in that the target organism becomes coated with antibodies; however, the target cell is destroyed by immune system cells that remain external to the target cell.

In **neutralization,** IgG antibodies inactivate microbes by blocking their attachment to host cells, and they neutralize toxins in a similar manner.

Finally, either IgG or IgM antibodies may trigger **activation of the complement system.** For example, inflammation is caused by infection or tissue injury (see Figure 16.9, page 454). One aspect of inflammation is that it will often cause microbes in the inflamed area to become coated with certain proteins. This, in turn, leads to the attachment to the microbe of an antibody–complement complex. This complex lyses the microbe, which then attracts phagocytes and other defensive immune system cells to the area. MM **Animation** Humoral Immunity: Antibody Function

CHECK YOUR UNDERSTANDING

Which antibodies may activate the complement system, and which antibodies are usually associated with agglutination? **17-11**

Cellular Immunity Response Process

LEARNING OBJECTIVES

17-12 Describe at least one function of each of the following: M cells, T_H cells, CTLs, T_{reg} cells, NK cells.

17-13 Differentiate T helper, T cytotoxic, and T regulatory cells.

17-14 Differentiate T_H1, T_H2, and T_H17 cells.

17-15 Define *apoptosis.*

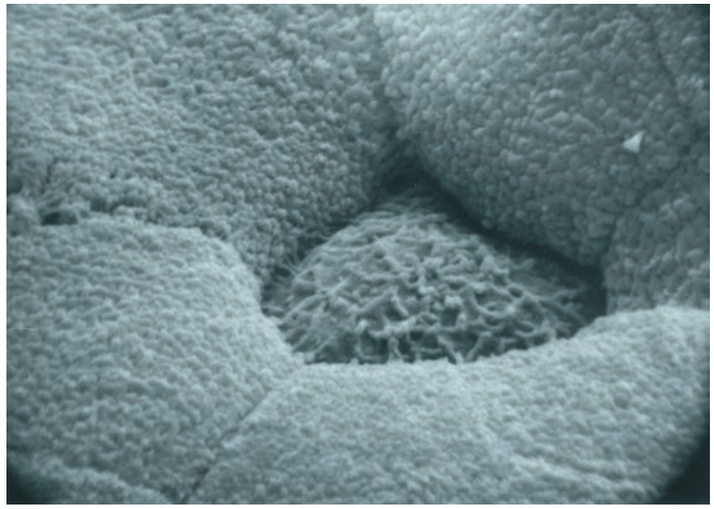
17-16 Define *antigen-presenting cell.*

Humoral antibodies are effective against pathogens such as viruses and bacteria that are circulating freely, where the antibodies can contact them. Intracellular antigens, such as a virus within an infected cell, are not exposed to circulating antibodies. Some bacteria and parasites can also invade and live within cells. T cells probably evolved in response to the need to combat intracellular pathogens. They are also the way in which the immune system recognizes cells that are abnormal, especially cancer cells.

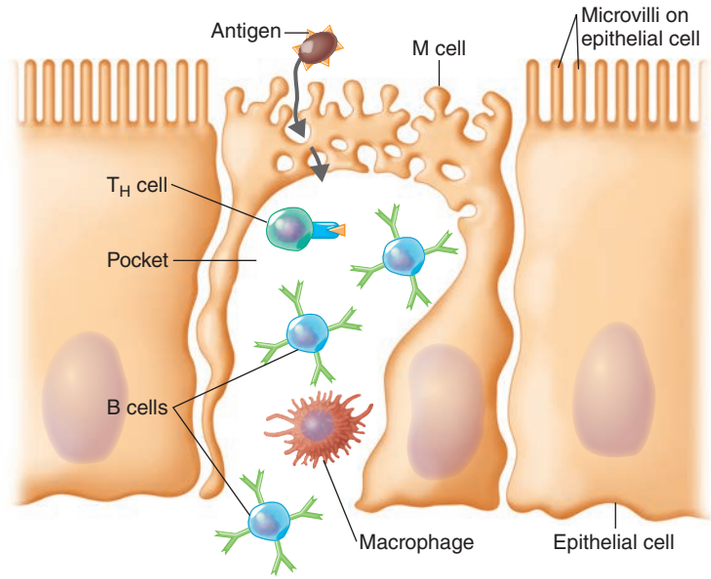
Like B cells, each T cell is specific for only a certain antigen. Rather than the coating of immunoglobulins that provide the specificity for B cells, T cells have T cell receptors (TCRs.)

Most immature T cells, an estimated 98%, are eliminated in the thymus, which is analogous to clonal deletion in B cells. This reflects a weeding-out process, called **thymic selection,** of T cells that will not recognize MHC molecules of the host and T cells that will attack host cells. This is important in preventing the body from attacking its own tissues. Next, mature T cells migrate from the thymus by way of the blood and lymphatic system to various lymphoid tissues (see Figure 16.5, page 448), where they are most likely to encounter antigens.

Most pathogens of the type that the cellular immune system is designed to combat first enter the gastrointestinal tract or lungs, where they encounter a barrier of epithelial cells. Normally, they can pass this barrier in the gastrointestinal tract only by way of a scattered array of gateway cells called **microfold cells,**



(a) M cell on Peyer's patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells. SEM 1 μm



(b) M cells facilitate contact between antigens passing through the intestinal tract and cells of the body's immune system.

Figure 17.9 M cells. M cells are located within Peyer's patches (see Figure 16.5, page 448), which are located on the intestinal wall. Their function is to transport antigens encountered in the digestive tract to contact lymphocytes and antigen-presenting cells (see page 480) of the immune system.

Q Why are M cells especially important for immune defenses against diseases affecting the digestive system?

or **M cells** (Figure 17.9; see also Figure 25.7, page 714). (Instead of the myriad of fingerlike microvilli found on the surface of absorptive epithelial cells of the intestinal tract, M cells have microfolds.) M cells are located over **Peyer's patches,** which are secondary lymphoid organs located on the intestinal wall. M cells are well adapted to take up antigens from the intestinal tract and allow their transfer to the lymphocytes and

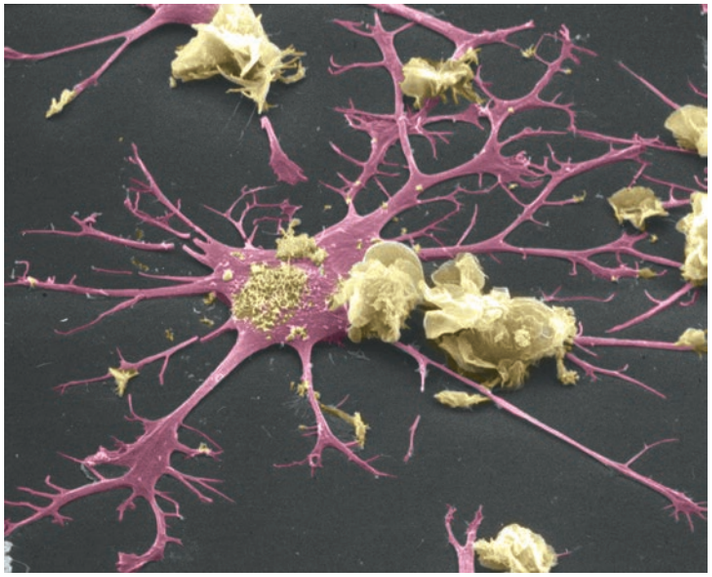


Figure 17.10 A dendritic cell. These cells link innate immunity and adaptive immunity by presenting antigens to T cells. The dendritic cell (pink) here is interacting with lymphocytes (yellow) that have been infected by a virus and are producing abnormal endogenous antigens.

Q What is the role of dendritic cells in immunity?

antigen-presenting cells of the immune system found throughout the intestinal tract, just under the epithelial-cell layer but especially in the Peyer's patches. It is also here that antibodies, mostly IgA essential for mucosal immunity, are formed and migrate to the mucosal lining.

Antigen-Presenting Cells (APCs)

B cells are a form of antigen-presenting cell (APC) that we have already discussed in the context of humoral immunity. Now we will consider APCs associated with cellular immunity. These APCs are the dendritic cells and the activated macrophages.

MM **Animation** Antigen Processing and Presentation: MHC

Dendritic Cells

Dendritic cells (DCs) are characterized by long extensions called dendrites (Figure 17.10) because they resemble the dendrites of nerve cells. They are the principal APCs to induce immune responses by T cells. The dendritic cells in the skin and genital tract are still called *Langerhans cells,* or *Langerhans DCs.* This represents only one of at least four populations of DCs named for their derivation or location. Other populations are found in the lymph nodes, spleen, thymus, blood, and various tissues—except the brain. Dendritic cells that act as sentinels in these tissues engulf invading microbes, degrade them, and transfer them to lymph nodes for display to T cells located there.

Macrophages

Macrophages (from the Greek for large eaters) are cells usually found in a resting state. We have already discussed the function of macrophages in phagocytosis. They are important for innate immunity and for ridding the body of worn-out blood cells (about 200 billion per day) and other debris, such as cellular remnants from apoptosis. Their phagocytic capabilities are greatly increased when they are stimulated to become **activated macrophages** (Figure 17.11). This activation can be initiated by ingestion of antigenic material. Other stimuli, such as cytokines produced by an activated T helper cell, can further enhance the capabilities of macrophages. Once activated, macrophages are more effective as phagocytes and as APCs. Activated macrophages are important factors in the control of cancer cells, virus-infected cells, and intracellular pathogens such as the tubercle bacillus. Their appearance becomes recognizably different as well—they are larger and become ruffled.

After taking up an antigen, APCs tend to migrate from their locations in virtually all tissues to lymph nodes or other lymphoid centers on the mucosa, where they present the antigen to T cells located there. T cells carrying receptors that are capable of binding with any specific antigen are present in relatively limited numbers. Migration of APCs increases the opportunity for these particular T cells to encounter the antigen for which they are specific.

Classes of T Cells

There are classes of T cells that have different functions, rather like the classes of immunoglobulins. As mentioned previously, **T helper cells (T_H)** cooperate with B cells in the production of antibodies, mainly through cytokine signaling. Therefore, T helper

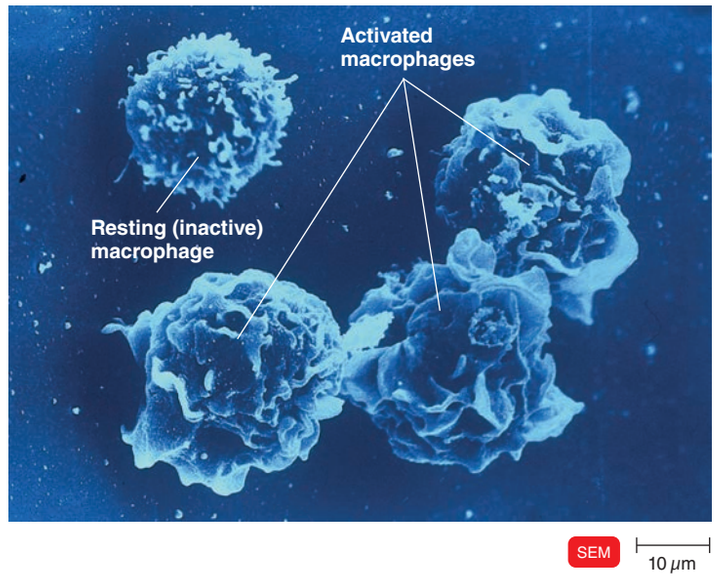


Figure 17.11 Activated macrophages. When activated, macrophages become larger and ruffled.

Q How do macrophages become activated?

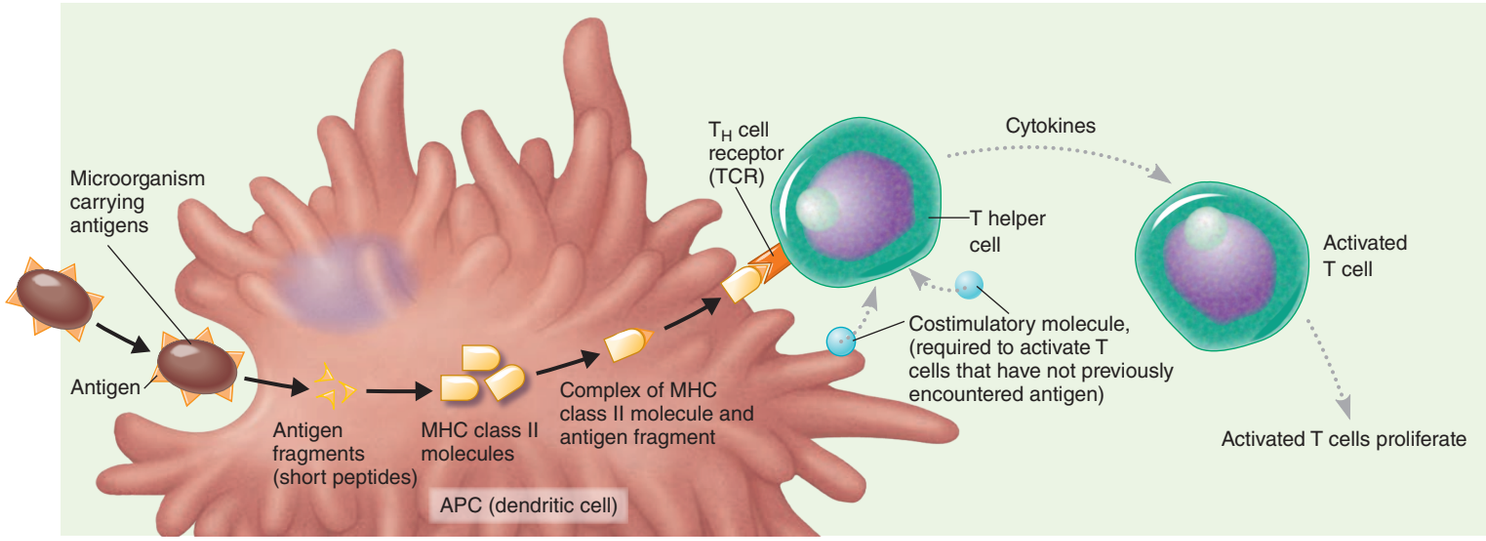


Figure 17.12 Activation of $CD4^+$ T helper cells. To activate a $CD4^+$ T helper cell, at least two signals are required: the first is the binding of the TCR to the processed antigen, and the second signal requires a costimulating cytokine, such as IL-2 and others. Once activated, the T_H cell secretes cytokines that affect the effector functions of multiple cell types of the immune system.

Q What is the role of the dendritic cell?

cells are an important part of humoral immunity—and they are an even more essential element of cellular immunity. In their contributions to cellular immunity, T cells interact more directly with antigens. In addition to T helper cells, there is a class of T cells called precursor **T cytotoxic cells ((CTLp).** A CTLp cell can differentiate into an effector cell called a **cytotoxic T lymphocyte (CTL).**

Clinical Case

The immune response to antigens takes place primarily in the secondary lymphoid organs, such as the lymph nodes, the mucosa-associated lymphoid tissue, and the spleen. During a primary immune response, pathogens and their constituents are transported to these tissues, where microbial antigens are presented to B cells that constantly enter and leave the secondary lymphoid organs. Dr. Marsden reviews her autopsy notes and sees that Mrs. Vasquez does not have a spleen; it had been removed following an automobile accident some years before.

Why is the fact that the patient has no spleen important?

469 470 474 477 481 484

T cells are also classified by certain glycoproteins on their surface called **clusters of differentiation,** or **CD.** These are membrane molecules that are especially important for adhesion to receptors. The CDs of greatest interest are CD4 and CD8; cells that carry these molecules are named **$CD4^+$** and **$CD8^+$** cells, respectively. (For the importance of these molecules in HIV infection, see Figure 19.13 on page 535.) T_H cells are classified as $CD4^+$, which bind to MHC class II molecules on B cells and APCs. CTL cells are classified as $CD8^+$, which bind to MHC class I molecules.

T Helper Cells ($CD4^+$ T Cells)

We have seen that an essential part of the body's innate defenses is phagocytosis by cells such as macrophages. T_H cells can recognize an antigen presented on the surface of a macrophage and activate the macrophage, making it more effective in both phagocytosis and in antigen presentation. Dendritic cells are especially important in the activation of $CD4^+$ T cells and in developing their effector functions (Figure 17.12).

For a $CD4^+$ T cell to become activated, its T cell receptor recognizes antigen fragments held in a complex with proteins of MHC class II on the surface of the APC. This is the initial signal for activation; a second signal, the costimulatory signal that comes from either the APC or T helper cell, is also required for activation. The activated T_H cell begins to proliferate at the rate

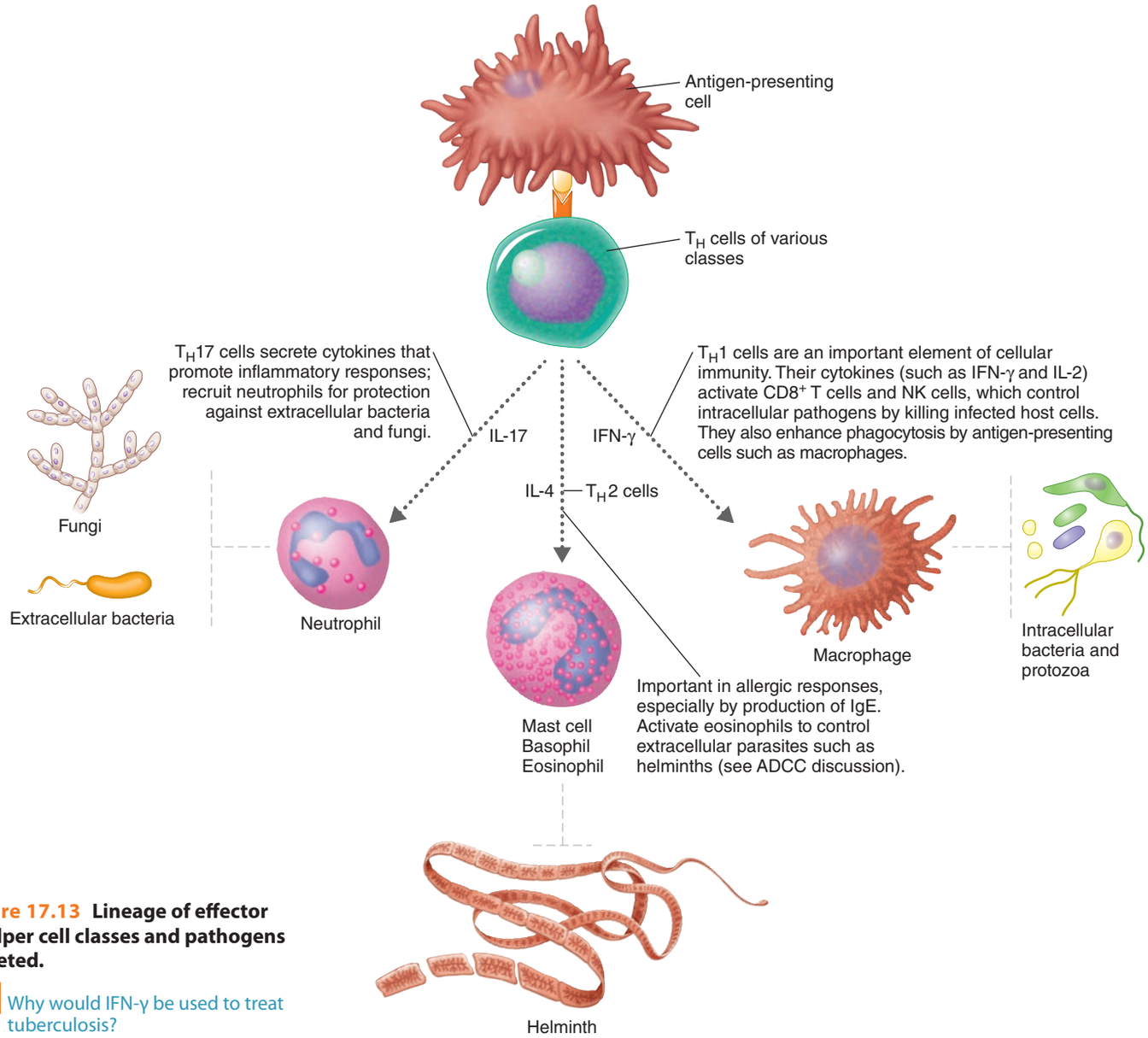


Figure 17.13 Lineage of effector T helper cell classes and pathogens targeted.

Q Why would IFN-γ be used to treat tuberculosis?

of two to three cell cycles a day and to secrete cytokines, which are essential for its effector functions. The proliferating T_H cells differentiate into populations of subsets such as T_H1, T_H2, and T_H17. They also form a population of long-lived memory cells. The effector functions of these subsets are based on the cytokines produced by these T_H cells, which act on different cells of the body's defensive systems.

At first it was thought there were only two subsets of T_H cells: T_H1 and T_H2. A third subset is named **T_H17** because of their production of large quantities of the cytokine IL-17. The discovery of T_H17 cells answered the questions raised by the observation that T_H1 and T_H2 cells were not effective in dealing with certain infections by extracellular bacteria and fungi. Excessive amounts of T_H17 cells probably contribute to the inflammation and injury to tissue found in certain autoimmune diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, and Crohn's disease. They are also probably associated with the pathologic effects of diseases such as asthma and allergic dermatitis. But they also serve, helpfully, to combat microbial infections of the mucosa by the production of cytokines such as IL-22, which stimulate epithelial cells to produce antimicrobial proteins. Therefore, a severe deficiency of T_H17 cells may make one more susceptible to opportunistic infections.

The functions of the three subsets directly involved in the body's defenses against external microbial threats are summarized in **Figure 17.13**, with their primary cytokine referenced in the figure. MM **Animation** Antigen Processing and Presentation: Steps

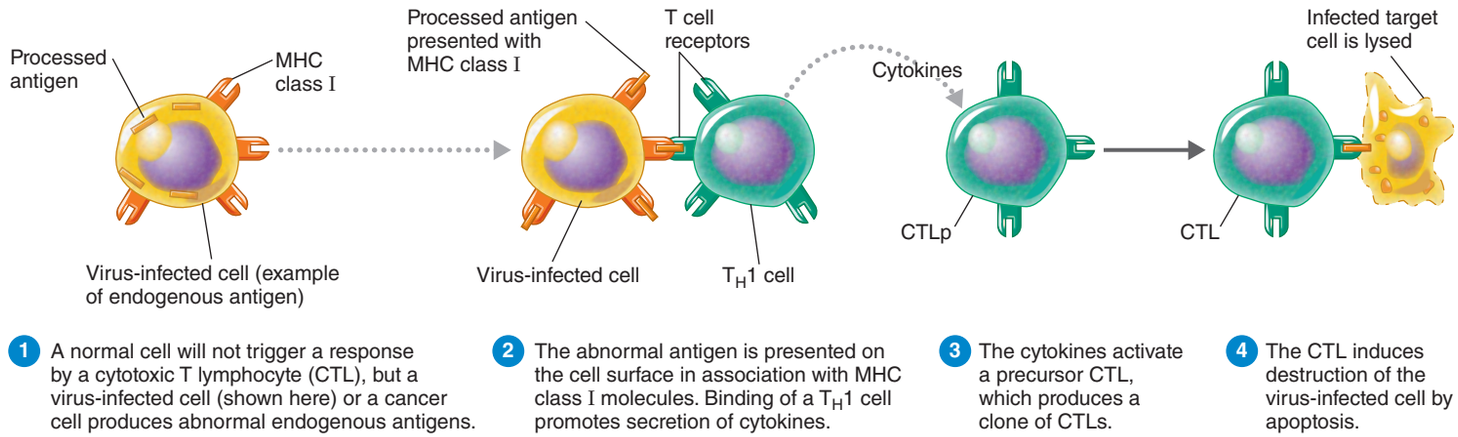


Figure 17.14 Killing of virus-infected target cell by cytotoxic T lymphocyte.

Q Differentiate a $CD8^+$ T cell from a $CD4^+$ T cell.

The cytokines produced by **T_H1 cells,** especially IFN-γ, activate mostly those cells related to important elements of cellular immunity, such as delayed hypersensitivity (see page 525), and are also responsible for activation of macrophages (see page 480). They also stimulate the production of antibodies that promote phagocytosis and are especially effective in enhancing the activity of complement, such as opsonization and inflammation (see Figure 16.12, page 459). As shown in **Figure 17.14**, the generation of cytotoxic T lymphocytes also requires action by a T_H1 cell.

T_H2 cells produce cytokines that are associated primarily with the production of antibodies, especially IgE, that are important in allergic reactions (see the discussion of hypersensitivity on page 516). They are also important in the activation of the eosinophils that defend against infections by extracellular parasites, such as helminths (see Figure 17.16 on page 485).

T Regulatory Cells

T regulatory cells (T_{reg}), formerly called *T suppressor cells,* make up about 5–10% of the T cell population. They are a subset of the $CD4^+$ T helper cells and are distinguished by carrying an additional CD25 molecule. Their primary function is to combat autoimmunity by suppressing T cells that escape deletion in the thymus without the necessary "education" to avoid reacting against the body's self. They are also useful in protecting, from the immune system, the intestinal bacteria required for digestion and other useful functions. Similarly, in pregnancy they may play a role in protecting the fetus from rejection as nonself. MM **Animation** Cell-Mediated Immunity: Cytotoxic T Cells

T Cytotoxic Cells ($CD8^+$ T Cells)

T cytotoxic cells, despite their name, are not capable of attacking any target cell as they emerge from the thymus but quickly attain this capability. This differentiation requires sequential, and complex, activation of the precursor CTL by an antigen processed by a dendritic cell and interaction with a T_H cell and costimulatory signals. The resulting CTL is an effector cell that has the ability to recognize and kill target cells that are considered nonself (see Figure 17.14). Primarily, these target cells are self-cells that have been altered by infection with a pathogen, especially viruses. On their surface they carry fragments of **endogenous antigens** that are generally synthesized within the cell and are mostly of viral or parasitic origin. Other important target cells are tumor cells (see Figure 19.11, page 532) and transplanted foreign tissue. Rather than reacting with antigenic fragments presented by an APC in complex with MHC class II molecules, the $CD8^+$ T cell recognizes endogenous antigens on the target cell's surface that are in combination with an MHC class I molecule. MHC class I molecules are found on nucleated cells; therefore, a CTL can attack almost any cell of the host that has been altered.

In its attack, a CTL attaches to the target cell and releases a pore-forming protein, **perforin.** Pore formation contributes to the subsequent death of the cell and is similar to the action of the complement membrane attack complex described in Chapter 16 (see page 458). **Granzymes,** proteases that induce apoptosis, are then able to enter through the pore.

Apoptosis (a-pah-TŌ-sis; from the Greek for falling away like leaves) is also called *programmed cell death*. The cell host has evolved mechanisms to detect the death of cells and to determine whether the death is natural, in which case no threat is involved and the remnants of the corpse are simply removed. However, if the cell's death is due to trauma or disease, the body's defense and repair mechanisms are mobilized. Therefore, if a cell cannot clear a pathogen in any other way, it clears it by dying—by apoptosis. For example, this prevents the spread of infectious viruses into other cells.

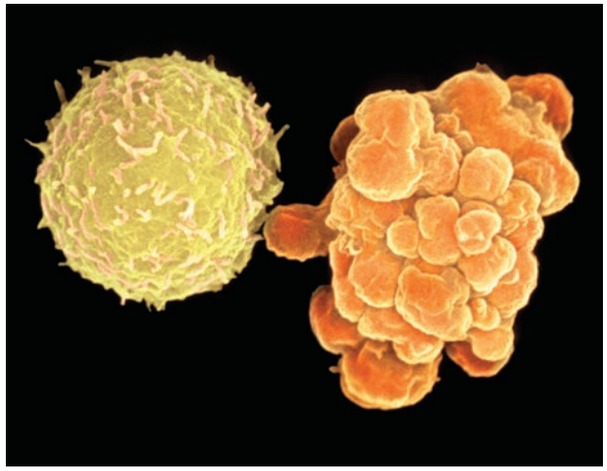


Figure 17.15 Apoptosis. A normal B cell is shown on the left. On the right, a B cell is undergoing apoptosis. Notice the bubble-like blebs.

Q What is apoptosis?

Cells that die from apoptosis first cut their genome into fragments, and the external membranes bulge outward in a manner called *blebbing* (Figure 17.15). Signals are displayed on the cell's surface that attract circulating phagocytes to digest the remains before any significant leakage of contents occurs.

Our bodies require apoptosis for other reasons, as well. It has been said that without apoptosis, the human body would accumulate 2 tons of bone marrow and lymph nodes and a 16-kilometer intestine by age 80.

Clinical Case Resolved

T cells, B cells, and dendritic cells are found in the spleen. In fact, about half of all blood lymphocytes circulate through the spleen each day. Normally, phagocytic cells of the spleen clear antibody- and complement-coated microorganisms very rapidly, thereby preventing the dissemination of infectious organisms to important organs. *Capnocytophaga* causes a range of infections from self-limiting cellulitis to fatal septicemia, but most fatal infections have occurred in asplenic persons, and 77% are associated with exposure to dogs. Unfortunately, Mrs. Vasquez contracted the infectious bacteria, and because her spleen had been removed some time before, she did not have the immune response necessary to combat the resulting deadly infection.

CHECK YOUR UNDERSTANDING

- What antibody is the primary one produced when an antigen is taken up by an M cell? **17-12**
- Which T cell type is generally involved when a B cell reacts with an antigen and produces antibodies against the antigen? **17-13**
- Which is the T cell type that is generally involved in allergic reactions? **17-14**
- What is another name for apoptosis, one that describes its function? **17-15**
- Are dendritic cells considered primarily part of the humoral or the cellular immune system? **17-16**

Extracellular Killing by the Immune System

LEARNING OBJECTIVE

17-17 Describe the function of natural killer cells.

We have seen how the action of a CTL can lead to the destruction of a target cell. A component of the innate immune system that has not yet been discussed can also destroy certain virus-infected cells and tumor cells. These are large granular leukocytes (10–15% of circulating lymphocytes) called **natural killer (NK) cells.** They can also attack parasites, which are normally much larger than bacteria, as illustrated in Figure 17.16. In contrast to CTLs, NK cells are not immunologically specific; that is, they do not need to be stimulated by an antigen. NK cells distinguish normal cells from transformed cells, or cells infected with intracellular pathogens. NK cells first contact the target cell and determine whether it expresses MHC class I self-antigens. If it does not—which is often the case in the early stages of viral infection and with some infecting viruses that have developed a system of interfering with the usual presentation of antigens on an APC—they kill the target cell by mechanisms similar to that of a CTL. Tumor cells also have a reduced number of MHC class I molecules on their surfaces. NK cells cause pores to form in the target cell, which leads to either lysis or apoptosis.

The functions of NK cells and the other principal cells involved in cellular immunity are briefly summarized in Table 17.2.

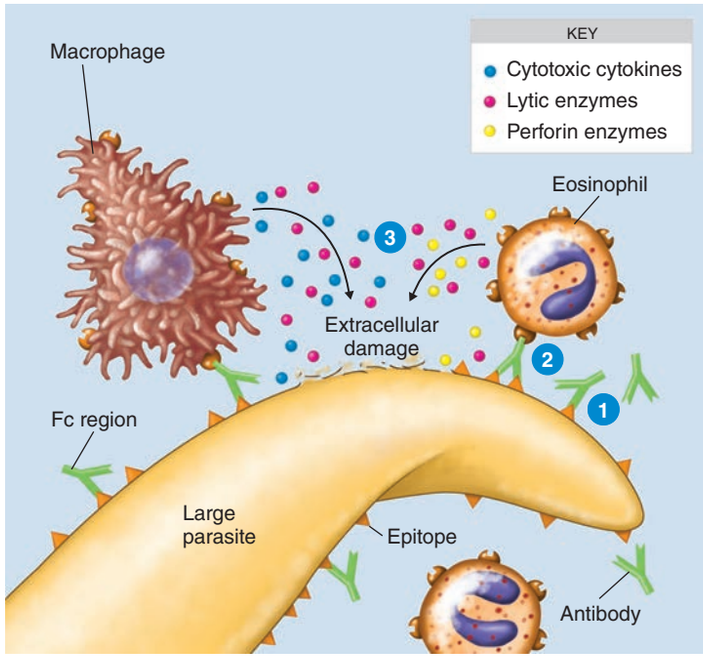
CHECK YOUR UNDERSTANDING

- How does the natural killer cell respond if the target cell does not have MHC class I molecules on its surface? **17-17**

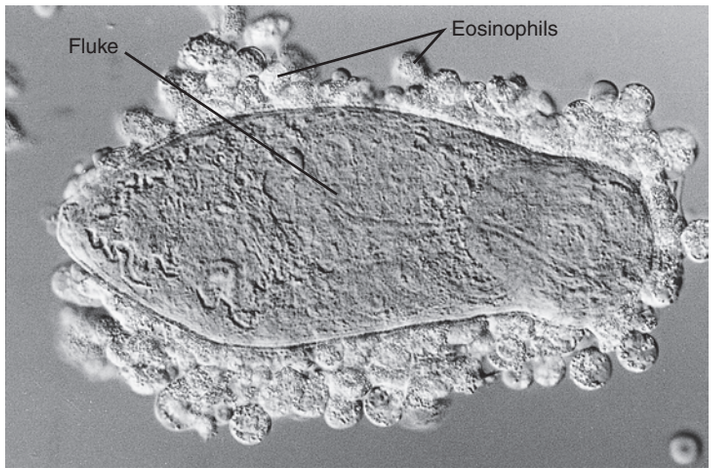
Antibody-Dependent Cell-Mediated Cytotoxicity

LEARNING OBJECTIVE

17-18 Describe the role of antibodies and natural killer cells in antibody-dependent cell-mediated cytotoxicity.



(a) Organisms, such as many parasites, that are too large for ingestion by phagocytic cells must be attacked externally.



(b) Eosinophils adhering to the larval stage of a parasitic fluke

Figure 17.16 Antibody-dependent cell-mediated cytotoxicity (ADCC). If an organism, such as a parasitic worm, is too large for ingestion and destruction by phagocytosis, it can be attacked by immune system cells that remain external to it. 1 The target cell is first coated with antibodies. 2 Cells of the immune system, such as eosinophils, macrophages, and NK cells (not shown), bind to the Fc regions of the attached antibodies. 3 The target cell is then lysed by substances secreted by the cells of the immune system.

Q Why is ADCC important protection against parasitic protozoa and helminths?

TABLE 17.2 Principal Cells That Function in Cell-Mediated Immunity

Cell	Function
T Helper (T_H1) Cell	Activates cells related to cell-mediated immunity: macrophages, T_C cells, and natural killer cells
T Helper (T_H2) Cell	Stimulates production of eosinophils, IgM, and IgE
T Helper (T_H17) Cell	Recruits neutrophils; stimulates production of antimicrobial proteins
Cytotoxic T Lymphocyte (CTL)	Destroys target cells on contact; generated from T cytotoxic (T_C) cell
T Regulatory (T_{reg}) Cell	Regulates immune response and helps maintain self-tolerance
Activated Macrophage	Enhanced phagocytic activity; attacks cancer cells
Natural Killer (NK) Cell	Attacks and destroys target cells; participates in antibody-dependent cell-mediated cytotoxicity

With the help of antibodies produced by the humoral immune system, the cell-mediated immune system can stimulate natural killer cells (see page 447) and cells of the innate defense system, such as macrophages, to kill targeted cells. In this way, an organism such as a protozoan or a helminth that is too large to be phagocytized can be attacked by immune system cells. This is referred to as **antibody-dependent cell-mediated cytotoxicity (ADCC).** As is illustrated in Figure 17.16, the target cell is first coated with antibodies. A variety of cells of the immune system bind to the Fc regions of these antibodies and, thus, to the target cell. The attacking cells secrete substances that then lyse the target cell.

CHECK YOUR UNDERSTANDING

What makes a natural killer cell, which is not immunologically specific, attack a particular target cell? **17-18**

Immunological Memory

LEARNING OBJECTIVE

17-19 Distinguish a primary from a secondary immune response.

The antibody-mediated immune responses of the host intensify after a second exposure to an antigen. This **secondary response** is also called the **memory (anamnestic) response.** As shown in Figure 17.17, this response is comparatively more rapid, reaching a peak in only 2 to 7 days, lasts many days, and is considerably greater in magnitude. By way of explanation, as is shown in Figure 17.5, some activated B cells do not become antibody-producing plasma cells but persist as long-lived but nonproliferating memory cells. Years, or even decades later, if these cells are

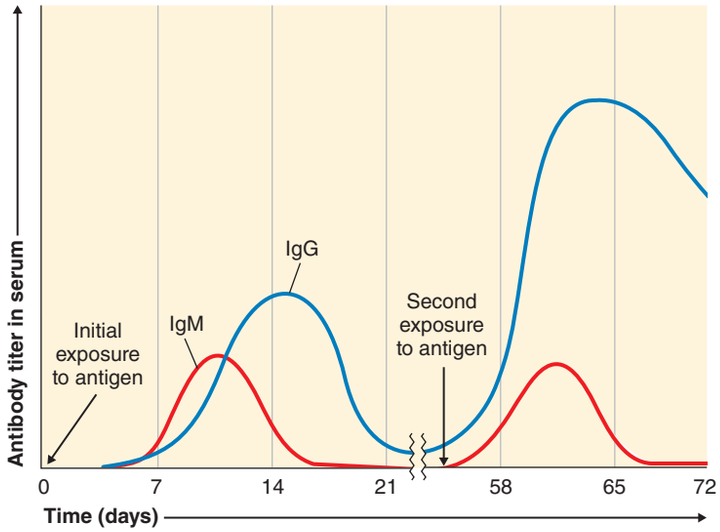


Figure 17.17 The primary and secondary immune responses to an antigen. IgM appears first in response to the initial exposure. IgG follows and provides longer-term immunity. The second exposure to the same antigen stimulates the memory cells (formed at the time of initial exposure) to rapidly produce a large amount of antibody. The antibodies produced in response to this second exposure are mostly IgG.

Q Why do many diseases, such as measles, occur only once in a person, yet others, such as colds, occur more than once?

stimulated by the same antigen, they very rapidly differentiate into antibody-producing plasma cells.

The intensity of the antibody-mediated humoral response can be reflected by the **antibody titer,** the relative amount of antibody in the serum. After the initial contact with an antigen, the exposed person's serum contains no detectable antibodies for 4 to 7 days. Then there is a slow rise in antibody titer: first, IgM class antibodies are produced, followed by IgG peaking in about 10 to 17 days, after which antibody titer gradually declines. This pattern is characteristic of a primary response to an antigen.

A similar response occurs with T cells, which, as we see in Chapter 19, is necessary for establishing the lifelong memory for distinguishing self from nonself. MM **Animations** Humoral Immunity: Primary Immune Response, Secondary Immune Response

CHECK YOUR UNDERSTANDING

Is the anamnestic response primary or secondary? **17-19**

Types of Adaptive Immunity

LEARNING OBJECTIVE

17-20 Contrast the four types of adaptive immunity.

Immunity can be acquired either actively or passively. Immunity is acquired *actively* when a person is exposed to microorganisms or foreign substances and the immune system responds. Immunity is acquired *passively* when antibodies are transferred from one person to another. Passive immunity in the recipient lasts only as long as the antibodies are present—in most cases, a few weeks. Both actively acquired immunity and passively acquired immunity can be obtained by natural or artificial means (Figure 17.18).

The four types of adaptive immunity can be summarized as follows:

- **Naturally acquired active immunity** develops when a person is exposed to antigens through everyday life, becomes ill, and then recovers. Once acquired, immunity is lifelong for some diseases, such as measles. For certain other diseases, especially intestinal diseases, the immunity may last for only a few years. *Subclinical infections* or *inapparent infections* (those that produce no noticeable symptoms or signs of illness) can also confer immunity.
- **Naturally acquired passive immunity** involves the natural transfer of antibodies from a mother to her infant. Antibodies in a pregnant woman cross the placenta to her fetus—*transplacental transfer.* If the mother is immune to diphtheria, rubella, or polio, for example, the newborn will be temporarily immune to these diseases as well. Certain antibodies are also passed from the mother to her nursing infant in breast milk, especially in the first secretions, called *colostrum.* In the infant, this passive immunity generally lasts only as long as the transmitted antibodies persist—usually a few weeks or months. These maternal antibodies are essential for providing immunity to the infant until its own immune system matures. Colostrum is even more important to some other mammals; calves, for example, do not have antibodies

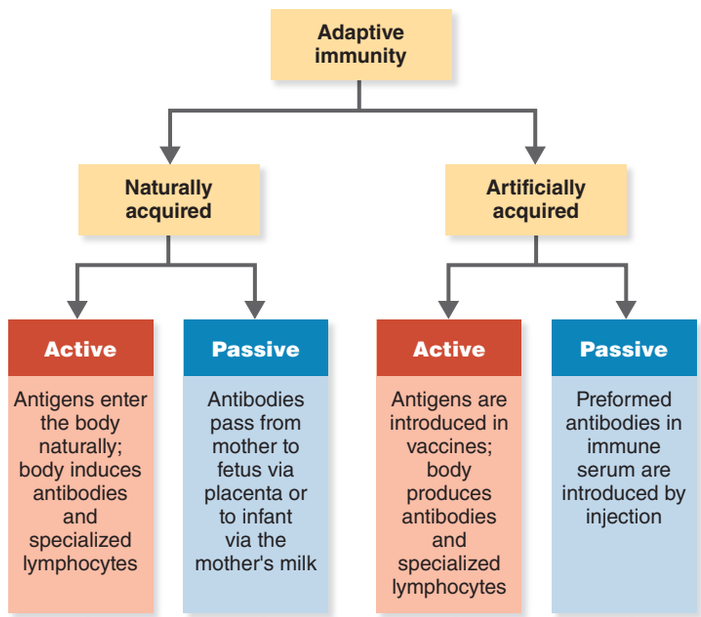


Figure 17.18 Types of adaptive immunity.

Q Which type of immunity, active or passive, lasts longer?

that cross the placenta and rely on colostrum ingested during the first day of life. Researchers often specify fetal calf serum for certain experimental uses because it does not contain maternal antibodies.

- **Artificially acquired active immunity** is the result of vaccination—which will be discussed in Chapter 18. **Vaccination,** also called **immunization,** introduces **vaccines** into the body. These are antigens, such as killed or living microorganisms or inactivated bacterial toxins.
- **Artificially acquired passive immunity** involves the injection of antibodies (rather than antigens) into the body. These antibodies come from an animal or a human who is already immune to the disease.

Because blood serum is easily obtained (see the Applications of Microbiology box in Chapter 16, page 462) and contains a considerable concentration of antibodies, **antiserum** has become a generic term for blood-derived fluids containing antibodies. Hence, the study of reactions between antibodies and antigens is called **serology.** As shown in **Figure 17.19**, when a sample of serum is subjected to an electrical current in the laboratory during gel electrophoresis (see Chapter 9), the proteins dissolved within it move at different rates. The globulin proteins separate into fractions that are termed alpha (α), beta (β), and gamma (γ) for their relative motility. Because the gamma fraction, called **gamma globulin,** contains most of the antibodies, it is often used to transfer passive immunity.

When gamma globulin, also called *immune serum globulin,* from an individual who is immune to a disease is injected into another individual, it confers an immediate passive protection against the disease. However, although artificially acquired passive immunity is immediate, it is short-lived because antibodies are degraded by the recipient. The half-life of an injected antibody (the time required for half of the antibodies to disappear) is typically about 3 weeks.

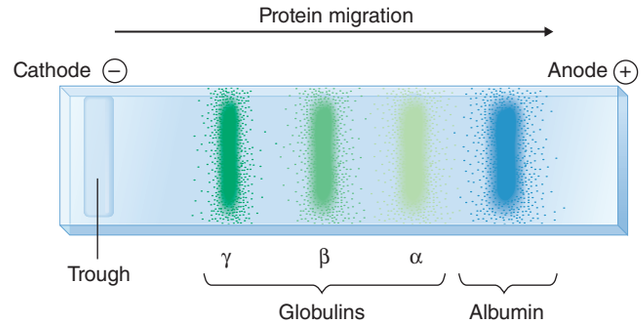


Figure 17.19 The separation of serum proteins by gel electrophoresis. In this procedure, serum is placed in a trough cut into an agar gel slab. In response to an electrical current, the negatively charged proteins of the serum migrate through the gel from the negatively charged end (cathode) to the positively charged end (anode).

Q What serum fraction contains the most antibodies?

CHECK YOUR UNDERSTANDING

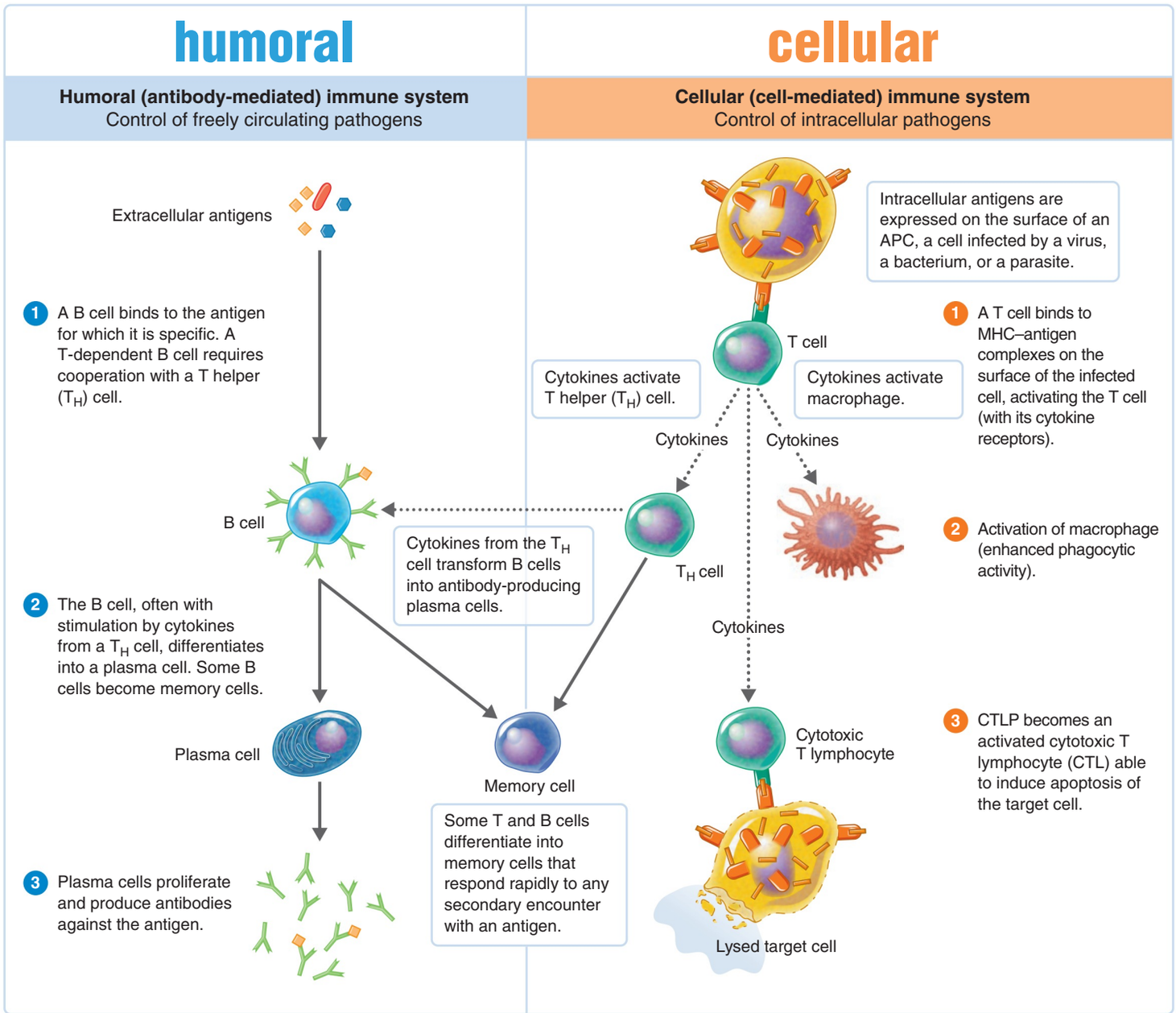
What type of adaptive immunity is involved when gamma globulin is injected into a person? **17-20**

* * *

This chapter on immunology is intended to provide you with the general concepts on the subject. It should give you the information you need to understand the chapters that follow, which emphasize some of the more practical and clinical aspects of immunology. Immunology can be a very complex subject; some of you, in pursuit of your academic major, will be taking a full course in immunology later and will study the subject in much more detail. The presentation here, you will then find, has been considerably simplified—although you might not have realized it. **Figure 17.20** summarizes the material covered in this chapter, especially emphasizing the dual nature of immunology.

FOUNDATION FIGURE 17.20

The Dual Nature of the Adaptive Immune System



KEY CONCEPTS

- The adaptive immune system is divided into two parts, each responsible for dealing with pathogens in different ways. These two systems function interdependently to keep the body free of pathogens.
- **Humoral immunity**, also called antibody-mediated immunity, is directed at freely circulating pathogens and depends on B cells.
- **Cellular immunity**, also called cell-mediated immunity, depends on T cells to eliminate intracellular pathogens, reject foreign tissue recognized as nonself, and destroy tumor cells.

Study Outline

MasteringMicrobiology®
Study microbiology where it matters: everywhere.
Check out the Study Area of MasteringMicrobiology to explore Interactive Microbiology. Study on-the-go with Dynamic Study Modules. Check Your understanding with chapter quizzes and animations—and much more!

The Adaptive Immune System (p. 469)

1. Adaptive immunity is the body's ability to react specifically to a microbial infection.
2. The body's response to the first contact with an antigen is called the primary response.
3. Subsequent contact with the same antigen results in a secondary or memory response to that antigen.

Dual Nature of the Adaptive Immune System (pp. 469–470)

1. Humoral immunity involves antibodies, which are found in serum and lymph and are produced by B cells.
2. Lymphocytes that mature in red bone marrow become B cells.
3. Cellular immunity involves T cells.
4. Lymphocytes that migrate through the thymus become T cells.
5. T cell receptors recognize antigens presented on MHC.
6. Cellular immunity responds to intracellular antigens; humoral immunity responds to antigens in body fluids.

Cytokines: Chemical Messengers of Immune Cells (pp. 470–471)

1. Cells of the immune system communicate with each other by means of chemicals called cytokines.
2. Interleukins (IL) are cytokines that serve as communicators between leukocytes.
3. Chemokines cause leukocytes to migrate to an infection.
4. Some interferons stimulate the immune response; others protect cells against viruses.
5. Tumor necrosis factor promotes the inflammatory reaction.
6. Hematopoietic cytokines promote development of white blood cells.
7. Overproduction of cytokines leads to a cytokine storm, which results in tissue damage.

Antigens and Antibodies (pp. 471–475)

Antigens (pp. 471–472)

1. An antigen (or immunogen) is a chemical substance that causes the body to produce specific antibodies.
2. As a rule, antigens are proteins or large polysaccharides. Antibodies are formed against specific regions on antigens called epitopes, or antigenic determinants.
3. A hapten is a low-molecular-weight substance that cannot cause the formation of antibodies unless combined with a carrier molecule; haptens react with their antibodies independently of the carrier molecule.

Antibodies (pp. 472–475)

4. An antibody, or immunoglobulin, is a protein produced by B cells in response to an antigen and is capable of combining specifically with that antigen.
5. Typical monomers consist of four polypeptide chains: two heavy chains and two light chains. They have two antigen-binding sites.
6. Within each chain is a variable (V) region that binds the epitope and a constant (C) region that distinguishes the different classes of antibodies.
7. An antibody monomer is Y-shaped or T-shaped: the V regions form the tips, and the C regions form the base and Fc (stem) region.
8. The Fc region can attach to a host cell or to complement.
9. IgG antibodies are the most prevalent in serum; they provide naturally acquired passive immunity, neutralize bacterial toxins, participate in complement fixation, and enhance phagocytosis.
10. IgM antibodies consist of five monomers held by a joining chain; they are involved in agglutination and complement fixation.
11. Serum IgA antibodies are monomers; secretory IgA antibodies are dimers that protect mucosal surfaces from invasion by pathogens.
12. IgD antibodies are on B cells; they may delete B cells that produce antibodies against self.
13. IgE antibodies bind to mast cells and basophils and are involved in allergic reactions.

Humoral Immunity Response Process (pp. 475–477)

1. B cells have antibodies on their surfaces, which recognize specific epitopes.
2. For T-independent antigens: a clone of B cells is selected by free antigens.
3. For T-dependent antigens: the B cell's immunoglobulins combine with an antigen, and the antigen fragments, combined with MHC class II, activate T_H cells. The T_H cells activate a B cell.
4. Activated B cells differentiate into plasma cells and memory cells.
5. Plasma cells produce IgM antibodies and then produce other classes, usually IgG.
6. B cells that recognize self are eliminated by clonal deletion.
7. Immunoglobulin genes in B cells recombine so that mature B cells each have different genes for the V region of their antibodies.

Antigen–Antibody Binding and Its Results (pp. 477–479)

1. An antigen–antibody complex forms when an antibody binds to its specific epitopes on an antigen.
2. Agglutination results when an antibody combines with epitopes on two different cells.
3. Opsonization enhances phagocytosis of the antigen.
4. Antibodies that attach to microbes or toxins and prevent them gaining access to the host or performing their action cause neutralization.
5. Complement activation results in cell lysis.

Cellular Immunity Response Process (pp. 479–484)

1. T cells mature in the thymus gland. Thymic selection removes T cells that don't recognize MHC molecules of the host and T cells that will attach host cells presenting self proteins in MHC.
2. Helper T cells recognize antigens processed by antigen-presenting cells and presented in MHC II.
3. Cytotoxic T cells recognize antigens processed by all host cells and presented in MHC I.

Antigen-Presenting Cells (APCs) (p. 480)

4. APCs include B cells, dendritic cells, and macrophages.
5. Dendritic cells are the primary APCs.
6. Activated macrophages are effective phagocytes and APCs.
7. APCs carry antigens to lymphoid tissues where T cells that recognize the antigen are located.

Classes of T Cells (pp. 480–484)

8. T cells are classified according to their functions and cell-surface glycoproteins called CDs.
9. T helper ($CD4^+$ T) cells differentiate into T_H1 cells, which are involved in cellular immunity; T_H2 cells, which are involved in humoral immunity and are associated with allergic reactions and parasitic infections; and T_H17 cells, which activate innate immunity.
10. T regulatory cells (T_{reg}) suppress T cells against self.
11. Cytotoxic lymphocytes (CTLs), or $CD8^+$ cells, are activated by endogenous antigens and MHC class I on a target cell and are transformed into effector and memory CTLs.
12. CTLs lyse or induce apoptosis in the target cell.

Extracellular Killing by the Immune System (p. 484)

1. Natural killer (NK) cells lyse virus-infected cells, tumor cells, and parasites. They kill cells that do not express MHC class I antigens.

Antibody-Dependent Cell-Mediated Cytotoxicity (pp. 484–485)

1. In antibody-dependent cell-mediated cytotoxicity (ADCC), NK cells and macrophages lyse antibody-coated cells.

Immunological Memory (pp. 485–486)

1. The relative amount of antibody in serum is called the antibody titer.
2. The peak IgG titer in the primary response occurs 10–17 days after exposure to an antigen.
3. The peak titer in the secondary response occurs 2–7 days after exposure.

Types of Adaptive Immunity (pp. 486–488)

1. Immunity resulting from infection is called naturally acquired active immunity; this type of immunity may be long-lasting.
2. Antibodies transferred from a mother to a fetus (transplacental transfer) or to a newborn in colostrum results in naturally acquired passive immunity in the newborn; this type of immunity can last up to a few months.
3. Immunity resulting from vaccination is called artificially acquired active immunity and can be long-lasting.
4. Artificially acquired passive immunity refers to humoral antibodies acquired by injection; this type of immunity can last for a few weeks.
5. Serum containing antibodies is often called antiserum.
6. When serum is separated by gel electrophoresis, antibodies are found in the gamma fraction of the serum and are termed immune serum globulin, or gamma globulin.

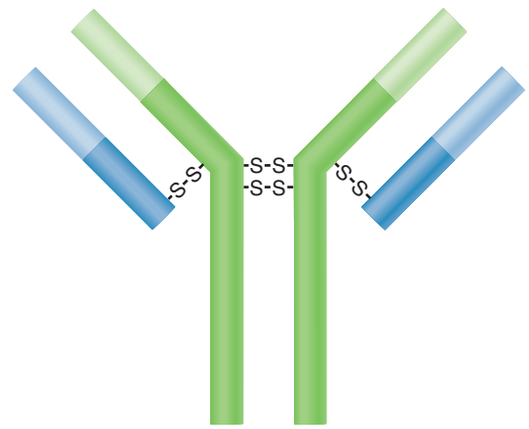
Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

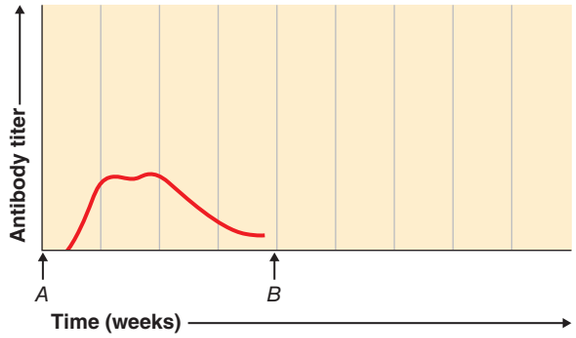
Review

1. Contrast the terms in the following pairs:
   - **a.** innate and adaptive immunity
   - **b.** humoral and cellular immunity
   - **c.** active and passive immunity
   - **d.** T_H1 and T_H2 cells
   - **e.** natural and artificial immunity
   - **f.** T-dependent and T-independent antigens
   - **g.** $CD8^+$ T cell and CTL
   - **h.** immunoglobulin and TCR
2. What does MHC stand for? What is the function of MHC? What types of T cells interact with MHC class I? With MHC class II?
3. DRAW IT Label the heavy chains, light chains, and variable and Fc regions of this typical antibody. Indicate where the antibody binds to antigen. Sketch an IgM antibody.



4. Diagram the roles that T cells and B cells play in immunity.
5. Explain a function for the following types of cells: CTL, T_H, and T_{reg}. What is a cytokine?

6. DRAW IT
   a. In the graph below, at time *A* the host was injected with tetanus toxoid. Show the response to a booster dose at time *B*.
   b. Draw the antibody response of this same individual to exposure to a new antigen indicated at time *B*.



7. How would each of the following prevent infection?
   a. antibodies against *Neisseria gonorrhoeae* fimbriae
   b. antibodies against host cell mannose
8. How can a human make over 10 billion different antibodies with only 35,000 different genes?
9. Explain why a person who recovers from a disease can attend others with the disease without fear of contracting it.
10. NAME IT This cell is found in skin and lymphoid tissue. It is a phagocyte and activates T cells.

Multiple Choice

Match the following choices to questions 1–4:

a. innate resistance
b. naturally acquired active immunity
c. naturally acquired passive immunity
d. artificially acquired active immunity
e. artificially acquired passive immunity

1. The type of protection provided by the injection of diphtheria toxoid.
2. The type of protection provided by the injection of antirabies serum.
3. The type of protection resulting from recovery from an infection.
4. A newborn's immunity to yellow fever.

Match the following choices to the statements in questions 5–7:

a. IgA
b. IgD
c. IgE
d. IgG
e. IgM

5. Antibodies that protect the fetus and newborn.
6. The first antibodies synthesized; especially effective against microorganisms.
7. Antibodies that are bound to mast cells and involved in allergic reactions.
8. Put the following in the correct sequence to elicit an antibody response: (1) T_H cell recognizes B cell; (2) APC contacts antigen; (3) antigen fragment goes to surface of APC; (4) T_H recognizes antigen digest and MHC; (5) B cell proliferates.
   a. 1, 2, 3, 4, 5
   b. 5, 4, 3, 2, 1
   c. 3, 4, 5, 1, 2
   d. 2, 3, 4, 1, 5
   e. 4, 5, 3, 1, 2
9. A kidney-transplant patient experienced a cytotoxic rejection of his new kidney. Place the following in order for that rejection: (1) apoptosis occurs; (2) $CD8^+$ T cell becomes CTL; (3) granzymes released; (4) MHC class I activates $CD8^+$ T cell; (5) perforin released.
   a. 1, 2, 3, 4, 5
   b. 5, 4, 3, 2, 1
   c. 4, 2, 5, 3, 1
   d. 3, 4, 5, 1, 2
   e. 2, 3, 4, 1, 5
10. Patients with Chédiak-Higashi syndrome suffer from various types of cancer. These patients are most likely lacking which of the following?
    a. T_{reg} cells
    b. T_H1 cells
    c. B cells
    d. NK cells
    e. T_H2 cells

Analysis

1. Injections of CTLs completely removed all hepatitis B viruses from infected mice, but they killed only 5% of the infected liver cells. Explain how CTLs cured the mice.
2. Why is dietary protein deficiency associated with increased susceptibility to infections?
3. A positive tuberculin skin test shows cellular immunity to *Mycobacterium tuberculosis*. How could a person acquire this immunity?
4. On her vacation to Australia, Janet was bitten by a poisonous sea snake. She survived because the emergency department physician injected her with antivenin to neutralize the toxin. What is antivenin? How is it obtained?

Clinical Applications and Evaluation

1. A woman had life-threatening salmonellosis that was successfully treated with anti-*Salmonella*. Why did this treatment work, when antibiotics and her own immune system failed?
2. A patient with AIDS has a low T_H cell count. Why does this patient have trouble making antibodies? How does this patient make *any* antibodies?
3. A patient with chronic diarrhea was found to lack IgA in his secretions, although he had a normal level of serum IgA. What was this patient found to be unable to produce?
4. Newborns (under 1 year) who contract dengue have a higher chance of dying from it if their mothers had dengue prior to pregnancy. Explain why.



In the Clinic

As the nurse in a vaccine clinic, you meet Eric, a healthy infant in for his 2-month appointment. His mother asks what vaccinations are due, and you explain that today Eric should receive his second dose of the hepatitis B vaccine, along with first doses of vaccinations designed to protect against rotavirus, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, pneumococcus, and polio. **Eric's mother is alarmed that her child must receive "so many shots all at once, when he is so little." How should you respond to her?**

Hint: Read about vaccines on page 493 and in Table 18.3.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

18 Practical Applications of Immunology

In Chapters 16 and 17, we learned the basics of the immune system, in which the body recognizes and defends against foreign microbes, toxins, or tissues. In this chapter, we will discuss some useful tools that have been developed from knowledge of the immune system. Vaccines were briefly mentioned in the previous chapter. The photograph shows a first line of defense, the human tracheal epithelium, colonized by *Bordetella pertussis* bacteria. The importance of vaccination against the disease caused by this pathogen is the focus of the chapter's Clinical Case. In this chapter, we will expand our discussion of the important field of immunology to address not only vaccines but also other practical applications. The diagnosis of disease, for example, frequently depends on tests that make use of antibodies and the specificity of the immune system.

Human tracheal epithelium, colonized by *Bordetella pertussis* bacteria.

Vaccines

LEARNING OBJECTIVES

18-1 Define *vaccine*.

18-2 Explain why vaccination works.

18-3 Differentiate the following, and provide an example of each: attenuated, inactivated, toxoid, subunit, and conjugated vaccines.

18-4 Contrast subunit vaccines and nucleic acid vaccines.

18-5 Compare and contrast the production of attenuated and killed vaccines, recombinant vaccines, and DNA vaccines.

18-6 Define *adjuvant*.

18-7 Explain the value of vaccines, and discuss acceptable risks for vaccines.

Long before the invention of vaccines, it was known that people who recovered from certain diseases, such as smallpox, were immune to the disease thereafter. Chinese physicians may have been the first to try to exploit this phenomenon to prevent disease when they had children inhale dried smallpox scabs.

In 1717, Lady Mary Montagu reported from her travels in Turkey that an "old woman comes with a nutshell full of the matter of the best sort of smallpox . . . and puts into the vein as much venom as can lie upon the head of her needle." This practice usually led to a week of mild illness, and the person was subsequently protected from smallpox. Called **variolation,** this procedure became commonplace in England. Unfortunately, however, it sometimes resulted in a serious case of smallpox. In eighteenth-century England, the mortality rate associated with variolation was about 1%, still a significant improvement over the 50% mortality rate that could be expected from smallpox. In 1840, the use of variolation was eventually prohibited.

Physician Edward Jenner began a series of experiments in 1798 in which he deliberately inoculated people with cowpox in an attempt to prevent smallpox. He did so because it had been observed that those infected by the mild disease did not contract smallpox later. Cowpox inoculation was safer than variolation and was used worldwide to prevent smallpox. To honor Jenner's work, Pasteur coined the term *vaccination* (from the Latin *vacca,* meaning cow).

A **vaccine** is a suspension of organisms or fractions of organisms that is used to induce immunity. Two centuries later, the disease of smallpox has been eliminated worldwide by vaccination, as has rinderpest, a viral disease of livestock. Measles, polio, and several other infectious diseases are also targeted for elimination. See the Clinical Focus box on page 498.

Animation Vaccines: Function

CHECK YOUR UNDERSTANDING

What is the etymology (origin) of the word *vaccine*? **18-1**

Principles and Effects of Vaccination

The development of vaccines based on the model of the smallpox vaccine is the single most important application of immunology. We now know that Jenner's inoculations worked because the cowpox virus, which is not a serious pathogen, is closely related to the smallpox virus. The injection, by skin scratches, provoked a primary immune response in the recipients, leading to the formation of antibodies and long-term memory cells. Later, when the recipient encountered the smallpox virus, the memory cells were stimulated, producing a rapid, intense secondary immune response (see Figure 17.17, page 486). This response mimics the immunity gained by recovering from the disease. The cowpox vaccine was soon replaced by a vaccinia virus vaccine. The vaccinia virus also confers immunity to smallpox, although, strangely, little is known with certainty about the origin of this important virus. It is genetically distinct from cowpox virus and may be a hybrid of an accidental mixing of cowpox and smallpox viruses or perhaps once may have been the cause of a now-extinct disease, horsepox.

Many communicable diseases can be controlled by behavioral and environmental methods. For example, proper sanitation can prevent the spread of cholera, and the use of condoms can slow the spread of sexually transmitted infections. If prevention fails, bacterial diseases can often be treated with antibiotics. Viral diseases, however, often cannot be effectively treated once contracted. Therefore, vaccination is frequently the only feasible method of controlling viral disease. Controlling a disease does not necessarily require that everyone be immune to it. If most of the population is immune, a phenomenon called **herd immunity,** outbreaks are limited to sporadic cases because there are not enough susceptible individuals to support the spread of epidemics.

The principal vaccines used to prevent bacterial and viral diseases in the United States are listed in **Table 18.1** and **Table 18.2**. Recommendations for childhood immunizations against some

Clinical Case: An Ounce of Prevention

Esther Kim, a 3-week-old infant girl, is brought to the emergency department by her parents. She has had a fever and cough for the last 5 days, but now she is coughing so hard that she is vomiting. Esther's 7-year-old brother, Mark, has also been ill with a runny nose and mild cough. The Kims did not think that Esther's illness was serious until she began vomiting. Dr. Roscelli, the resident physician, admits baby Esther to the hospital for tests and observation; she is hospitalized for 5 days.

What infection does Esther have? Read on to find out.

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TABLE 18.1 Principal Vaccines Used in the United States to Prevent Bacterial Diseases in Humans

Disease(s)	Vaccine	Recommendation	Booster
Haemophilus influenzae type b meningitis	Polysaccharide from *Haemophilus influenzae* type b conjugated with protein to enhance effectiveness	Children prior to school age; see Table 18.3	None recommended
Meningococcal meningitis	Purified polysaccharide from *Neisseria meningitidis*	For people with substantial risk of infection; recommended for college freshmen, especially if living in dormitories	Need not established
Pneumococcal pneumonia	Purified polysaccharide from seven strains of *Streptococcus pneumoniae*	For adults with certain chronic diseases; people over 65; children 2–23 months	None if first dose administered ≥ 24 months
Tetanus, diphtheria, and pertussis	DTaP (children younger than 3), Tdap (older children and adults), Td (booster for tetanus and pertussis)	DTaP (months 2, 4, 6, 15–18; years 4–6);* Td (adults every 10 years); Tdap (similar to Td; single dose for children aged 11–12 years, or adults); booster every 10 years	Tdap (booster) every 10 years

*For details, see www.cdc.gov

TABLE 18.2 Principal Vaccines Used in the United States to Prevent Viral Diseases in Humans

Disease	Vaccine	Recommendation	Booster
Chickenpox	Attenuated virus	For infants aged 12 months.	(Duration of immunity not known)
Hepatitis A	Inactivated virus	Mostly for travel to endemic areas and protecting contacts during outbreaks..	Duration of protection estimated at about 10 years
Hepatitis B	Antigenic fragments of virus	For infants and children, see Table 18.3; for adults, especially health care workers, homosexual men, injecting drug users, heterosexual people with multiple partners, and household contacts of hepatitis B carriers.	Duration of protection at least 7 years; need for boosters uncertain
Herpes zoster	Attenuated virus	Adults over age 60.	None recommended
Human papillomavirus	Antigenic fragments of virus	Boys and girls ages 11-12.	Duration at least 5 years
Influenza	Injected vaccine, inactivated virus (nasally administered vaccine with attenuated virus is now available for some)	For chronically ill, including children over 6 months. Adults over age 65. Healthy children aged 6–23 months (because higher risk of related hospitalizations). Health care workers and others in contact with high risk groups. Healthy persons aged 5–49 years can receive intranasal vaccine.	Annual
Measles	Attenuated virus	For infants aged 15 months.	Adults if exposed during outbreak
Mumps	Attenuated virus	For infants aged 15 months.	Adults if exposed during outbreak
Poliomyelitis	Killed virus	For children, see Table 18.3; for adults, as risk to exposure warrants.	(Duration of immunity not known)
Rabies	Killed virus	For field biologists in contact with wildlife in endemic areas; for veterinarians; for people exposed to rabies virus by bites.	Every 2 years
Rotavirus	Rota Teq, modified rotaviruses; Rotarix vaccine, attenuated strain	Oral, for infants up to 8 months	None recommended
Rubella	Attenuated virus	For infants aged 15 months; for women of childbearing age who are not pregnant.	Adults if exposed during outbreak
Smallpox	Live vaccinia virus	Certain military and health care personnel.	Duration of protection estimated at about 3 to 5 years

TABLE 18.3 Recommended Immunization Schedule for Persons Aged 0–12 Years—United States, 2014 (CDC)

Vaccine ▼	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years	11–12 years
Hepatitis B	HepB	HepB			HepB							
Rotavirus			Rv	Rv	Rv							
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP		DTaP				DTaP	
***Haemophilus influenzae* type b**			Hib	Hib	Hib	Hib						
Pneumococcal*			PCV	PCV	PCV	PCV				PPSV		
Inactivated Poliovirus			IPV	IPV		IPV					IPV	
Influenza					Influenza (Yearly)							
Measles, Mumps, Rubella						MMR					MMR	
Varicella						Varicella					Varicella	
Hepatitis A†						HepA (2 doses)						
Meningococcal‡										MCV		
Human Papillomavirus§												HPV

Note: Vaccines are listed under routinely recommended ages. Shaded bars indicate range of recommended ages for immunization. For those who fall behind or start late, see the catch-up schedule. Additional information at www.cdc.gov

* PCV = Pneumococcal conjugate vaccine, PPSV = Pneumococcal polysaccharide vaccine.

† The two doses at least 6 mo. apart.

‡ Meningococcal conjugate vaccine (MCV) for children aged 2–10 years with defective immune systems and certain other high risk situations.

§ Three doses over a 6-month period between the ages of 11 and 12.

of these diseases are given in Table 18.3. American travelers who might be exposed to cholera, yellow fever, or other diseases not endemic in the United States can obtain current immunization recommendations from the U.S. Public Health Service and local public health agencies.

CHECK YOUR UNDERSTANDING

Vaccination is often the only feasible way to control most viral diseases; why is this? **18-2**

Types of Vaccines and Their Characteristics

There are several basic types of vaccines. Some newer vaccines take full advantage of knowledge and technology developed in recent years.

Live Attenuated Vaccines

Deliberate weakening, called *attenuation,* can lead to the production of live **attenuated vaccines**. When the practice of cell culture for producing viruses for study came into use, it was realized an extended period of cell culture was, itself, a means to attenuate pathogenic viruses. This finding expanded the number of preventable diseases, especially for humans.

Live vaccines closely mimic an actual infection. As the pathogen reproduces within the host cells, cellular, as well as humoral, immunity usually is induced. Lifelong immunity, especially in the case of viruses, is often achieved without booster immunizations, and an effectiveness rate of 95% is not unusual. This long-term effectiveness probably occurs because the attenuated viruses replicate in the body, increasing the original dose and acting as a series of secondary (booster) immunizations.

Inactivated Killed Vaccines

Inactivated killed vaccines use microbes that have been killed, usually by formalin or phenol. Inactivated virus vaccines used in humans include those against rabies, influenza (Figure 18.1), and polio (the Salk polio vaccine). Generally speaking, these vaccines are considered safer than live vaccines. Inactivated



Figure 18.1 Influenza viruses are grown in embryonated eggs. (See Figure 13.7, page 367.) The viruses will be inactivated to make a vaccine.

Q Could this method of viral cultivation be a problem for people who are allergic to eggs?

bacterial vaccines include those for pneumococcal pneumonia and cholera. Compared to live attenuated vaccines, these inactivated vaccines often require repeated booster doses. They also induce a mostly humoral antibody immunity, which makes them less effective than attenuated vaccines in inducing cellular immunity. Several long-used inactivated vaccines are being replaced for most uses by newer, more effective types; examples include the vaccines for pertussis (whooping cough) and typhoid.

Subunit Vaccines

Subunit vaccines use only those antigenic fragments of a microorganism that best stimulate an immune response. This avoids the dangers associated with the use of live or killed pathogenic organisms. Subunit vaccines that are produced by genetic modification techniques—meaning that other microbes are programmed to produce the desired antigenic fraction—are called **recombinant vaccines.** For example, the vaccine against the hepatitis B virus consists of a portion of the viral protein coat that is produced by a genetically modified yeast (see Chapter 8).

Virus-like particle (VLP) vaccines resemble intact viruses but do not contain any viral genetic material. The vaccine for the hepatitis B virus is an example—it consists of a portion of the protein coat of the virus that is produced by a genetically modified yeast. Vaccines for human papillomavirus (HPV), which causes many cervical cancers and genital warts, are also VLP vaccines.

Toxoids, which are inactivated toxins, are vaccines directed at the toxins produced by a pathogen. The tetanus and diphtheria toxoids have long been part of the standard childhood immunization series. The person requires a series of injections to attain full immunity, followed by boosters every 10 years. Many older adults have not received boosters; they are likely to have low levels of protection. Before antibiotics were available to treat diphtheria, the disease was treated with **antitoxins,** that is, serum containing antibodies against the toxin. A disease for which this treatment is still used is tetanus. It can provide protection against tetanus toxin when there is danger of tetanus and the patient has not had a current tetanus vaccination.

Some pathogens, most notably *Streptococcus pneumoniae* (pneumococcus), are virulent primarily because their polysaccharide capsule makes them resistant to phagocytosis. The vaccine used against pneumococcal pneumonia targets this capsule. A vaccine for *Neisseria meningitidis* uses a similar mechanism.

Conjugated Vaccines

Conjugated vaccines have been developed in recent years to deal with the poor immune response of children to vaccines based on capsular polysaccharides. Polysaccharides are T-independent antigens, and children's immune systems do not respond well to these antigens until the age of 15–24 months (see Figure 17.7, page 477). The polysaccharides are combined with proteins such as diphtheria or tetanus toxoid; this approach has led to the very successful vaccine for *Haemophilus influenzae* type b (Hib), which gives significant protection even at 2 months.

Nucleic Acid (DNA) Vaccines

Nucleic acid vaccines, often called *DNA vaccines,* are among the newest and most promising vaccines. Experiments with animals show that plasmids of "naked" DNA injected into muscle results in the production of the protein antigen encoded in the DNA. The injection can be made by conventional needle or, more efficiently, by the "gene gun" method described in Chapter 9, page 245, and Figure 9.6, which delivers the vaccine into many skin cell nuclei. The protein antigens are carried to the red bone marrow and stimulate both humoral and cellular immunity. They also tend to be expressed for extended times, with good immunological memory. However, vaccines based on polysaccharide capsules of bacteria cannot be made by this method.

Two DNA vaccines for animals have been approved: one that protects horses from West Nile virus, and another that protects domestically reared salmon from a serious viral disease. Clinical tests in humans are under way testing DNA vaccines for a number of different diseases; human immunization with some of these vaccines can be expected in the next few years. Such vaccines would have particular advantages for the less developed parts of the world. The "gene gun" would eliminate the need for large supplies of syringes and needles, and these vaccines would not require refrigeration. Manufacturing operations for such vaccines are very similar for different diseases, which should lower costs. MM **Animation** Vaccines: Types

Clinical Case

Dr. Roscelli examines Esther every day she is in the hospital. At no time does he wear a face mask. Dr. Roscelli does not suspect pertussis (whooping cough) until the attending physician suggests that he swab Esther's throat and request a PCR test for the bacteria. Sure enough, Esther's throat swab is positive for *Bordetella pertussis* DNA.

Why do you think Dr. Roscelli did not suspect pertussis when Esther was admitted to the ER?

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CHECK YOUR UNDERSTANDING

- Experience has shown that attenuated vaccines tend to be more effective than inactivated vaccines. Why? **18-3**
- Which is more likely to be useful in preventing a disease caused by an encapsulated bacterium such as the pneumococcus: a subunit vaccine or a nucleic acid vaccine? **18-4**

The Development of New Vaccines

An effective vaccine is the most desirable method of disease control. It prevents the targeted disease from ever occurring at all in an individual, and it is generally the most economical. This is especially important in developing parts of the world.

Although interest in vaccine development declined with the introduction of antibiotics, it has intensified in recent years. Fear of litigation contributed to the decrease in the development of new vaccines in the United States. However, passage of the National Childhood Vaccine Injury Act in 1986, which limits the liability of vaccine manufacturers, has helped reverse this trend. Even so, for pharmaceutical companies the most profitable drugs are those that must be taken daily for extended periods, for example, drugs taken for diabetes or high blood pressure. In contrast, a vaccine that is required for a few injections or even only once in a lifetime is less attractive to create because the potential profit is less.

Historically, vaccines often could be developed only by growing the pathogen in usefully large amounts in animals; for example, the vaccinia virus for smallpox was grown on the shaved bellies of calves. Unfortunately, many viruses that cause human diseases will not grow in animals. The introduction of vaccines against polio, measles, mumps, and a number of other viral diseases awaited the development of cell culture techniques. Cell cultures from human sources or, more often, from animals that are closely related to humans, such as monkeys, enabled growth of these viruses on a large scale. A convenient animal that will grow many viruses is the chick embryo (see Figure 13.7, page 367). Viruses for several vaccines (influenza, for example) are grown this way (see Figure 18.1). Interestingly, the first vaccine against hepatitis B virus used viral antigens extracted from the blood of chronically infected humans because no other source was available.

Recombinant vaccines and DNA vaccines do not need a cell or animal host to grow the vaccine's microbe. This avoids a major problem with certain viruses that so far do not grow well in cell culture—hepatitis B, for example.

Plants are also a potential source for vaccines. Already, human trials have been conducted with potatoes that have been engineered to produce antigenic proteins from certain pathogenic bacteria and viruses. It is more likely, however, that plants for this purpose will not be used directly as food, but as a production system for doses of antigenic proteins that would be taken orally as pills. Tobacco plants are a leading candidate for this use because they are unlikely to contaminate the food chain.

Oral vaccines are favored for many reasons even beyond eliminating a need for injections. For one, they would be especially effective in protecting against the diseases caused by pathogens invading the body through the mucous membranes. Examples of current oral vaccines include ones for polio, rotavirus, adenovirus, and cholera. Oral vaccines for tuberculosis, *C. difficile,* and influenza are being developed. For influenza, there is also an intranasal spray vaccine that allows some people to avoid injections.

The so-called golden age of immunology occurred from about 1870 to 1910, when most of the basic elements of immunology were discovered and several important vaccines were developed. We may soon be entering another golden age, in which new technologies are brought to bear on emerging infectious diseases and problems arising from the decreasing effectiveness of antibiotics. It is remarkable that there are no useful vaccines against chlamydias, fungi, protozoa, or helminthic parasites of humans. Moreover, vaccines for some diseases, such as cholera and tuberculosis, are not reliably protective. At present, vaccines for many diseases are under development, ranging from those for prominent deadly diseases such as AIDS and malaria to such commonplace conditions as earaches. But we will probably find that the easy vaccines have already been made.

Infectious diseases are not the only possible target of vaccines. Researchers are investigating vaccines' potential for treating and preventing cocaine addiction, Alzheimer's disease, cancer, and even for contraception.

Most current vaccines act by causing the production of humoral antibodies. There is a need for vaccines that confer T cell–based immunity, which would be especially useful against tuberculosis, HIV, and cancer. Antigenic variability also remains a problem; for example, the influenza virus changes character each year and requires a new vaccine annually. As a practical matter, if the antigen changes more rapidly than once a year—HIV, for example, changes its antigenic structure daily—it cannot

CLINICAL FOCUS

A World Health Problem

As you read through this box, you will encounter a series of questions that public health scientists ask themselves as they try to reduce the occurrence of diseases. Try to answer each question before going to the next one.

1. Maria, a 17-year-old girl, returned home to the United States from a church trip to Rome. Soon after, she developed a fever and tiny red spots with blue-white centers inside her mouth (**Figure A**). Two days later, she developed a rash on her face, which then spread to her trunk and extremities. Subsequently, 2 year-old Joanie, a little girl from Maria's church, developed a fever and was diagnosed with pneumonia. In all, 34 people from Maria's church developed a maculopapular rash, fever (≥38°C), and at least one of the following: cough, conjunctivitis, or coldlike symptoms.

   What was the disease? (*Hint:* See Diseases in Focus 21.1 on page 584.)

2. Testing for IgM measles antibodies confirmed the diagnosis of measles. Measles is a highly contagious viral illness that can cause pneumonia, diarrhea, encephalitis, and death.

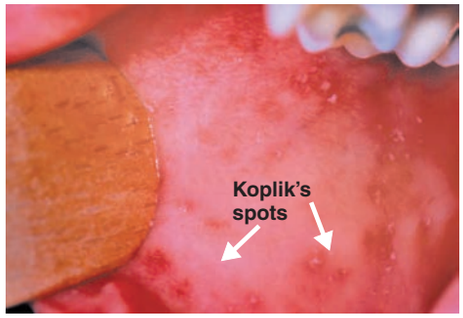


Figure A **Koplik's spots inside the cheeks.**

How did Maria contract measles?

3. Maria had traveled to Italy for 2 weeks with her church group. She and the other infected people had not been vaccinated against measles.

Why didn't more people get measles?

4. In 1920, before the measles vaccine was developed, nearly 500,000 cases of measles occurred, with over 7500 deaths, in the United States. In 2013, only 184 cases of measles were reported in the United States (**Figure B**). However, measles still occurs

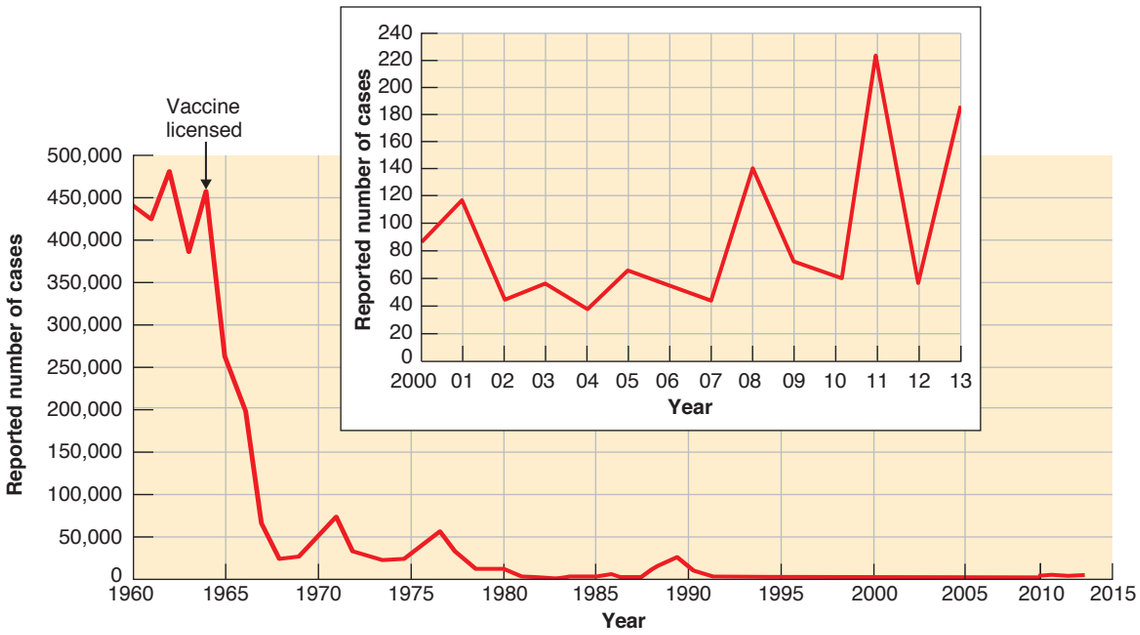


Figure B **Reported numbers of measles cases in the United States, 1960–2013 (CDC, 2014).**

be controlled by conventional vaccines. Computers now allow us to search the structure of the antigen's genome for protective antigens. This "reverse vaccinology" is becoming an essential tool for vaccine development.

Vaccination Technologies

In many cases today, especially in less-developed regions, minimally trained personnel are called on to vaccinate large numbers of people. This lack of training and resources poses problems with injected vaccines: single-use doses can be expensive, and sterilization for reusable needles may be uncertain. So other delivery methods are being explored. One alternative method under development is a skin patch (Nanopatch) that administers a dry formulation of a vaccine. Skin tissue contains a high number of antigen-presenting cells—more than the muscle tissue reached by conventional needles. Another advantage is that dry vaccines such as the skin patch require no refrigeration. This is especially important; the World Health Organization estimates that half the vaccines used in Africa are ineffective because of faulty refrigeration of vials of injectable vaccines.

Even in the developed world, the sheer number of injections required for infants and children makes creating more multiple-combination vaccines desirable. The U.S. Food and Drug Administration (FDA) recently approved a new combination vaccine for pertussis, diphtheria, tetanus, polio, and *Haemophilus influenzae* type b (Hib).

in many countries (**Figure C**). Worldwide, there were 20 million cases in 2012, resulting in 330 deaths every day.

What would happen if we stopped vaccinating against measles?

5. If there were no vaccines, there would be many more cases of disease. Along with more disease, there would be serious sequelae and more deaths. Some vaccine-preventable diseases are still quite prevalent in other parts of the world. As occurred in this case, travelers can unknowingly bring these diseases into the United States, and if we were not protected by vaccinations, these diseases could quickly spread throughout the population, causing epidemics here.

The Measles Initiative is a partnership—led by the American Red Cross, the United Nations Foundation, UNICEF, the U.S. Centers for Disease Control and Prevention, and the World Health Organization—committed to reducing measles deaths worldwide. The Measles Initiative has supported the vaccination of nearly 1 billion children in over 50 countries. In 2000, measles caused approximately 757,000 deaths, mostly in children under 5. By 2011, measles deaths were reduced to 158,000 people worldwide.

Source: Adapted from *MMWR* 62(36): 741–743, September 13, 2013.

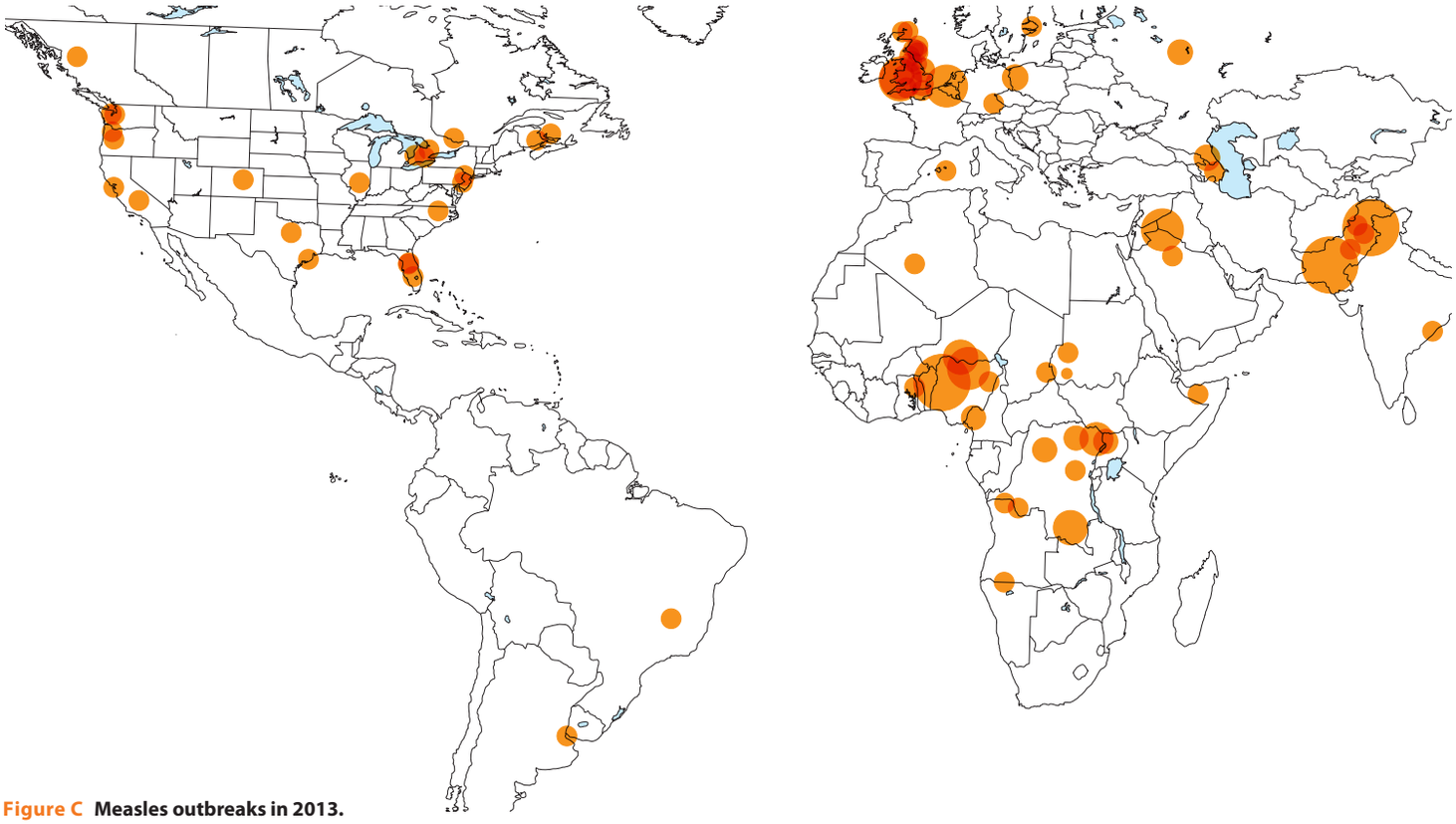


Figure C Measles outbreaks in 2013.

Adjuvants

The early days of commercial vaccine production saw occasional problems with contamination. Unexpectedly, once the contamination was corrected it was found that the purified vaccine was often less effective. This led to experiments designed to determine whether chemical additives could improve effectiveness. An imaginative assortment of substances (some as bizarre as tapioca) were tried for this purpose. This led to the chance discovery that certain aluminum salts improved vaccine effectiveness. Generally grouped under the term *alum*, these aluminum salts, called **adjuvants,** are combined with many vaccines. At this time, alum is the only adjuvant approved for use in humans in the United States. (The reason is that the United States is considered "more litigious," according to one school of thought.) Other adjuvants, such as MF59 (an oil-and-water emulsion) are used in Europe and elsewhere. Some adjuvants are approved only for use in animals. The exact mechanism by which adjuvants work is not known in all detail, but they are known to improve the innate immune response, especially activation of Toll-like receptors.

CHECK YOUR UNDERSTANDING

- Which type of vaccine is a live measles virus: inactivated, attenuated, recombinant, or DNA? **18-5**
- What is the value of an *adjuvant*? **18-6**

Clinical Case

Vaccination has been so successful in reducing childhood infections that many younger physicians have never seen a case of pertussis. Nine days after initial exposure to Esther's illness, Dr. Roscelli exhibits a runny nose and, 4 days later, a cough. Dr. Roscelli assumes he has a cold and declines recommended prophylaxis with erythromycin. Further investigation identifies seven other pertussis cases in health care workers (a respiratory therapist, a radiologic technician, and five student nurses), all of whom work in the emergency department but not in pediatrics.

How did Dr. Roscelli and the seven health care workers get the infection?

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Safety of Vaccines

We have seen how variolation, the first attempt to provide immunity to smallpox, sometimes *caused* the disease it was intended to prevent. At the time, however, the risk was considered very worthwhile. Safety issues still arise. For example, the oral polio vaccine on rare occasions may cause the disease. In 1999, a vaccine to prevent infant diarrhea caused by rotaviruses was withdrawn from the market because several recipients developed a life-threatening intestinal obstruction. However, public reaction to such risks has changed; most parents have never seen a case of polio or measles and therefore tend to view the risk of a vaccine side effect as more worrisome than the risk of the disease itself. Moreover, reports or rumors of harmful effects often lead people to avoid certain vaccines for themselves or their children. In particular, a connection between the MMR vaccine and autism has received widespread publicity. The journal that first published the study that ignited this controversy later retracted it, and the chief scientist who conducted the research later lost his medical license under accusations of fraud. But because autism is a poorly understood developmental condition that is usually diagnosed at the age of 18 to 30 months, about the time immunization schedules are nearing completion, some people have attempted to make a cause-and-effect connection. Medically, however, most experts agree that autism is a condition with a major genetic component and begins before birth. Extensive scientific surveys have provided no evidence to support a connection between the usual childhood vaccines and autism or any other disease condition. Some experts even recommend again introducing the rotavirus vaccine that was withdrawn in the United States, maintaining that it would be well justified on a risk-versus-benefit calculation in much of the underdeveloped world. No vaccine will ever be perfectly safe or perfectly effective—nor is any antibiotic or most other drugs, for that matter. Nevertheless, vaccines still remain the safest and most effective means of preventing infectious disease in children.

CHECK YOUR UNDERSTANDING

- Why could the oral (Sabin) polio vaccine sometimes cause polio, but the injected (Salk) vaccine does not? **18-7**

Diagnostic Immunology

LEARNING OBJECTIVES

18-8 Differentiate sensitivity from specificity in a diagnostic test.
18-9 Define *monoclonal antibodies,* and identify their advantage over conventional antibody production.
18-10 Explain how precipitation reactions and immunodiffusion tests work.
18-11 Differentiate direct from indirect agglutination tests.
18-12 Differentiate agglutination from precipitation tests.
18-13 Define *hemagglutination.*
18-14 Explain how a neutralization test works.
18-15 Differentiate precipitation from neutralization tests.
18-16 Explain the basis for the complement-fixation test.
18-17 Compare and contrast direct and indirect fluorescent-antibody tests.
18-18 Explain how direct and indirect ELISA tests work.
18-19 Explain how Western blotting works.
18-20 Explain the importance of monoclonal antibodies.

Throughout most of history, diagnosing a disease was essentially a matter of observing a patient's signs and symptoms. The writings of ancient and medieval physicians left descriptions of many diseases that are recognizable even today. Essential elements of diagnostic tests are sensitivity and specificity. **Sensitivity** is the probability that the test is reactive if the specimen is a true positive. **Specificity** is the probability that a positive test will *not* be reactive if a specimen is a true negative.

Immunologic-Based Diagnostic Tests

Knowledge of the high specificity of the immune system soon suggested that this might be used in diagnosing diseases. In fact, it was an accidental observation that led to one of the first diagnostic tests for an infectious disease. More than 100 years ago, Robert Koch was trying to develop a vaccine against tuberculosis. He observed that when guinea pigs with the disease were injected with a suspension of *Mycobacterium tuberculosis,* the site of the injection became red and slightly swollen a day or two later. You may recognize this symptom as a positive result for the widely used tuberculin skin test (see Figure 24.9, page 687)—many colleges and universities require the test as part of admission procedures. Koch, of course, had no idea of the mechanism

of cell-mediated immunity that caused this phenomenon, nor did he know of the existence of antibodies.

Immunology has given us many other invaluable diagnostic tools, most of which are based on interactions of humoral antibodies with antigens. A known antibody can be used to identify an *unknown* pathogen (antigen) by its reaction with it. This reaction can be reversed, and a *known* pathogen can be used, for example, to determine the presence of an unknown antibody in a person's blood—which would determine whether he or she had immunity to the pathogen. One problem that must be overcome in antibody-based diagnostic tests is that antibodies cannot be seen directly. Even at magnifications of well over 100,000×, they appear only as fuzzy, ill-defined particles (see Figure 17.4c on page 473). Therefore, their presence must be established indirectly. We will describe a number of ingenious solutions to this problem.

Other problems that had to be overcome were that antibodies produced in an animal were mixed with numerous other antibodies produced in that animal and the quantities of any particular antibody were severely limited.

CHECK YOUR UNDERSTANDING

What property of the immune system suggested its use as an aid for diagnosing disease: specificity or sensitivity? **18-8**

Monoclonal Antibodies

As soon as it was determined that antibodies were produced by B cells, it was understood that these were a potential source of a single type of antibody. If such a B cell producing a single type of antibody could be isolated and cultivated, it would be able to produce the desired antibody in nearly unlimited quantities and without contamination by other antibodies. Unfortunately, a B cell reproduces only a few times under the usual cell culture conditions. This problem was largely solved by tapping cancerous antibody-producing B cells for culture.

These cancerous B cells, known as *myelomas,* can be isolated and propagated indefinitely in cell culture. Combining an "immortal" cancerous B cell with an antibody-producing normal B cell creates a **hybridoma.**

When a hybridoma is grown in culture, its genetically identical cells continue to produce the type of antibody characteristic of the ancestral B cell indefinitely, producing immense quantities of identical antibody molecules. Because all of these antibody molecules are produced by a single hybridoma clone, they are called **monoclonal antibodies,** or **Mabs** (Figure 18.2).

Monoclonal antibodies are uniform, are highly specific, and can be produced in large quantities. Because of these qualities, Mabs have assumed enormous importance as diagnostic tools. For instance, commercial kits use Mabs to recognize several bacterial pathogens, and nonprescription pregnancy tests use Mabs to indicate the presence of a hormone excreted only in the urine of a pregnant woman (see Figure 18.13, page 510).

Monoclonal antibodies have become a clinically important, and frequently used, class of drugs. Currently more than 25 Mabs have been approved for human therapy. These include treatments for multiple sclerosis, Crohn's disease, psoriasis, cancer, asthma, and arthritis. There are many Mabs currently being developed worldwide for a wide range of diseases and conditions.

The mechanisms of therapeutic action of Mabs vary. Certain inflammatory diseases such as rheumatoid arthritis require the action of tumor necrosis factor (TNF; see page 453). Mabs that neutralize TNF block the progression of the disease. One such Mab is infliximab (Remicade). Other Mabs block a receptor site; an example is omalizumab (Xolair). This drug treats allergic asthma by preventing the binding of IgE on mast cells and basophils (see Figure 19.1 on page 517). The Mab rituximab (Rituxan) is used to treat inflammatory diseases that the TNF-blocking Mabs cannot. This class of Mab binds to antigen-bearing cells, depleting their supply and thereby blocking the progression of the disease.

The therapeutic use of Mabs had been limited because these antibodies once were produced only by mouse (murine) cells. The immune systems of some patients reacted against the foreign mouse proteins, leading to rashes, swelling, and even occasional kidney failure, plus the destruction of the Mabs.

In recognition of this problem, researchers are developing new generations of Mabs that are less likely to cause side effects due to "foreignness." Essentially, the more human the antibody, the more successful it is likely to be. Researchers are exploring several approaches.

Chimeric monoclonal antibodies use genetically modified mice to make a human–murine hybrid. (A *chimera* is an animal or tissue made up of elements derived from genetically distinct individuals, in this case a human and a mouse. The term comes from the mythological monster that had a lion's head, goat's body, and serpent's tail.) The variable part of the antibody molecule, including the antigen-binding sites (see Figure 17.4a on page 473), is murine. The remainder of the antibody molecule, the constant region, has been derived from a human source. These Mabs are about 66% human. An example is rituximab, which treats leukemias and some autoimmune disorders that are characterized by excessive numbers of B cells.

Minimizing the murine component of chimeric Mabs lessens the immune response against the Mab in humans. This is the aim of **humanized antibodies** constructed so the murine portion is limited to antigen-binding sites, with the rest of the molecule (about 90%) being derived from human sources. An example is trastuzumab (Herceptin), which treats breast cancers.

Even humanized antibodies can cause unwanted immune responses, which has spurred research and development of **fully human antibodies.** One approach has been to genetically modify mice so they contain human antibody genes. An early fully human Mab is adalimumab (Humira), used to treat rheumatoid arthritis and psoriatic arthritis.

FOUNDATION FIGURE 18.2

The Production of Monoclonal Antibodies

1. A mouse is injected with a specific antigen that will induce production of antibodies against that antigen.

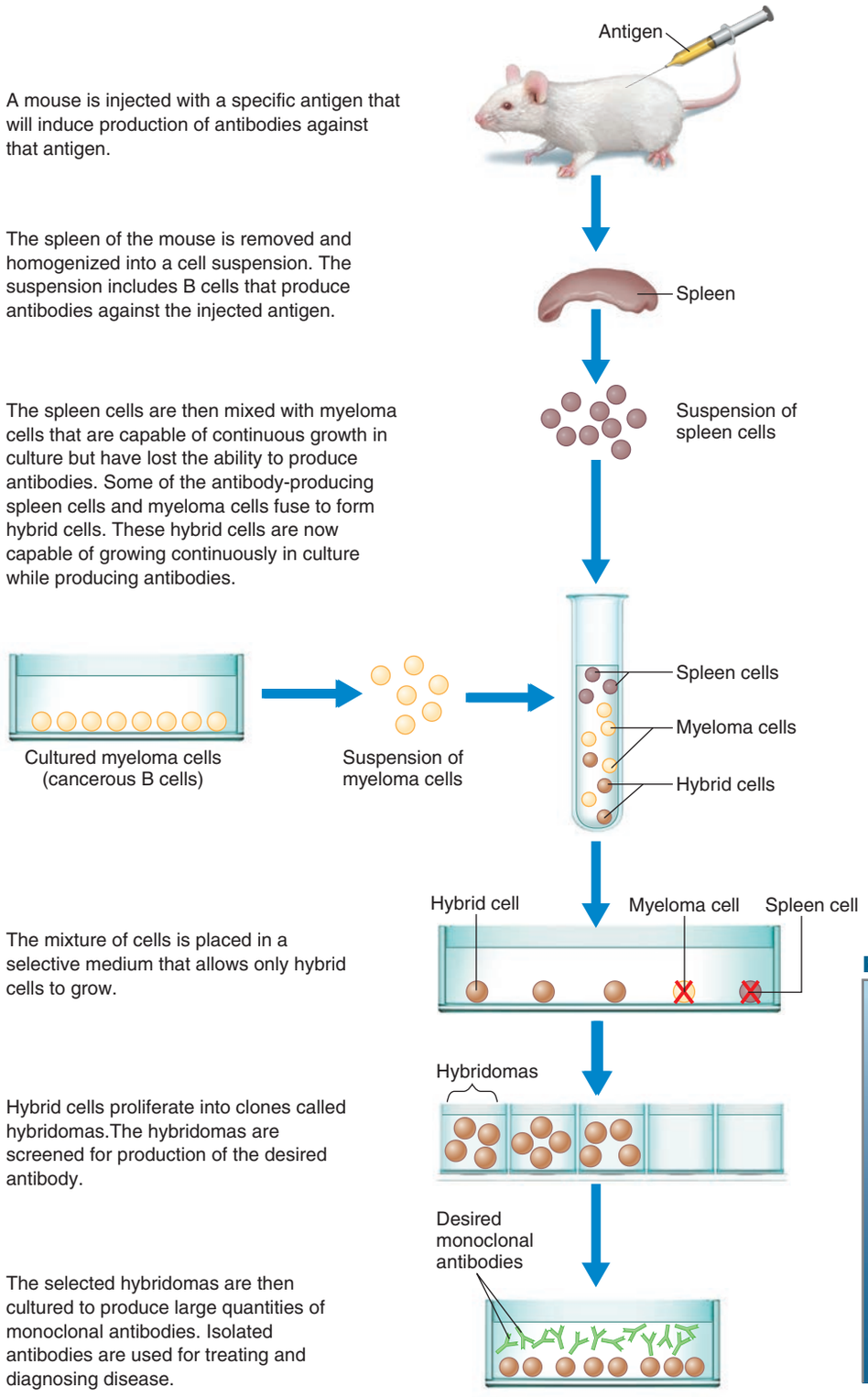
2. The spleen of the mouse is removed and homogenized into a cell suspension. The suspension includes B cells that produce antibodies against the injected antigen.

3. The spleen cells are then mixed with myeloma cells that are capable of continuous growth in culture but have lost the ability to produce antibodies. Some of the antibody-producing spleen cells and myeloma cells fuse to form hybrid cells. These hybrid cells are now capable of growing continuously in culture while producing antibodies.

4. The mixture of cells is placed in a selective medium that allows only hybrid cells to grow.

5. Hybrid cells proliferate into clones called hybridomas.The hybridomas are screened for production of the desired antibody.

6. The selected hybridomas are then cultured to produce large quantities of monoclonal antibodies. Isolated antibodies are used for treating and diagnosing disease.



KEY CONCEPTS

- The fusion of cultured myeloma cells (cancerous B cells) with antibody-producing spleen cells forms a hybridoma.
- Hybridomas can be cultured to produce large quantities of identical antibodies, called monoclonal antibodies.
- Monoclonal antibody production is an important advancement in medicine and also is integral to common diagnostic and therapeutic tools. A monoclonal antibody can attach to a target cell while carrying a diagnostic marker or an anticellular toxin.

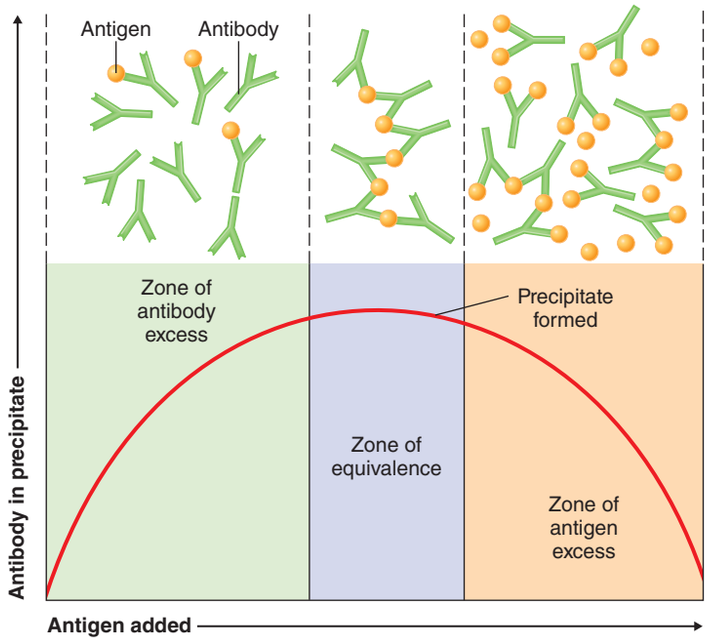


Figure 18.3 A precipitation curve. The curve is based on the ratio of antigen to antibody. The maximum amount of precipitate forms in the zone of equivalence, where the ratio is roughly equivalent.

Q How does precipitation differ from agglutination?

The source of particular Mabs can be recognized from the spelling of the final letters of the name: human (*u*), mouse (*o*), chimera (*xi*), or humanized (*zu*). For example, a name ending in *-umab* shows that the Mab is derived from a human source. Other endings are *-zumab* (humanized), *-omab* (mouse), and *-ximab* (chimera). The spelling may also point to the general disease state or particular tumors that the Mab treats. The spelling of biciromab shows that this Mab is derived from a mouse (*-omab*) and directed at treating a cardiovascular condition (indicated by the letters *cir*). Mabs are used in the diagnostic tests described throughout the rest of this chapter.

CHECK YOUR UNDERSTANDING

The blood of an infected cow would have a considerable amount of antibodies against the infectious pathogen in its blood. How would an equivalent amount of monoclonal antibodies be more useful? **18-9**

Precipitation Reactions

Precipitation reactions involve the reaction of soluble antigens with IgG or IgM antibodies to form large, interlocking molecular aggregates called *lattices.*

Precipitation reactions occur in two distinct stages. First, the antigens and antibodies rapidly form small antigen–antibody complexes. This interaction occurs within seconds and is followed by a slower reaction, which may take minutes to hours, in which the antigen–antibody complexes form lattices that precipitate from solution. Precipitation reactions normally occur only when the ratio of antigen to antibody is optimal. **Figure 18.3** shows that no visible precipitate forms when either component is in excess. The optimal ratio is produced when separate solutions of antigen and antibody are placed adjacent to each other and allowed to diffuse together. In a **precipitin ring test** (**Figure 18.4**), a cloudy line of precipitation (ring) appears in the area in which the optimal ratio has been reached (the *zone of equivalence*).

Immunodiffusion tests are precipitation reactions carried out in an agar gel medium, on either a Petri plate or a microscope slide. A line of visible precipitate develops between the wells at the point where the optimal antigen–antibody ratio is reached.

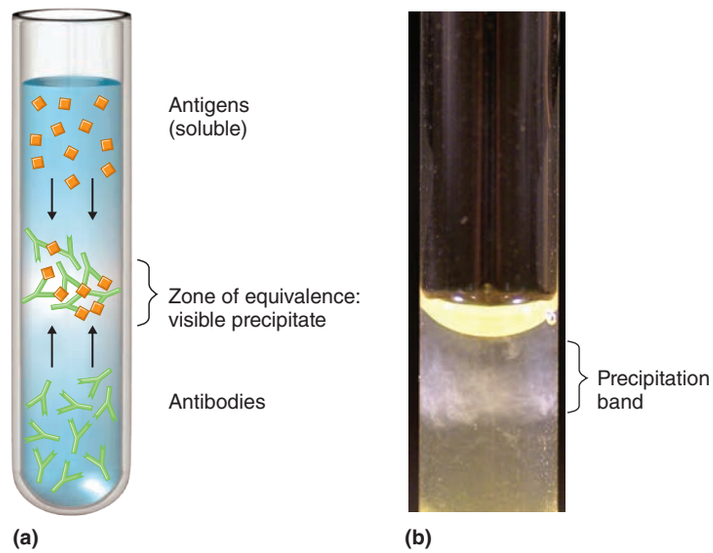


Figure 18.4 The precipitin ring test. **(a)** This drawing shows the diffusion of antigens and antibodies toward each other in a small-diameter test tube. Where they reach equal proportions, in the zone of equivalence, a visible line or ring of precipitate is formed. **(b)** A photograph of a precipitin band.

Q What causes the visible line?

Clinical Case

Dr. Roscelli did not wear a mask at any time he examined Esther, and consequently he contracted pertussis. He should have worn a mask to prevent transmission of respiratory infections; he also should have accepted antibiotic treatment for his symptoms. Dr. Roscelli could have transmitted the infection to his colleagues in the emergency department, and, in turn, the infected hospital personnel could have transmitted pertussis to vulnerable patients. When investigating Esther's illness, health care workers discover that neither Esther nor her brother has been vaccinated. The Kims were fearful because they had heard that vaccinations could cause serious side effects and even death.

Did the Kims make a mistake?

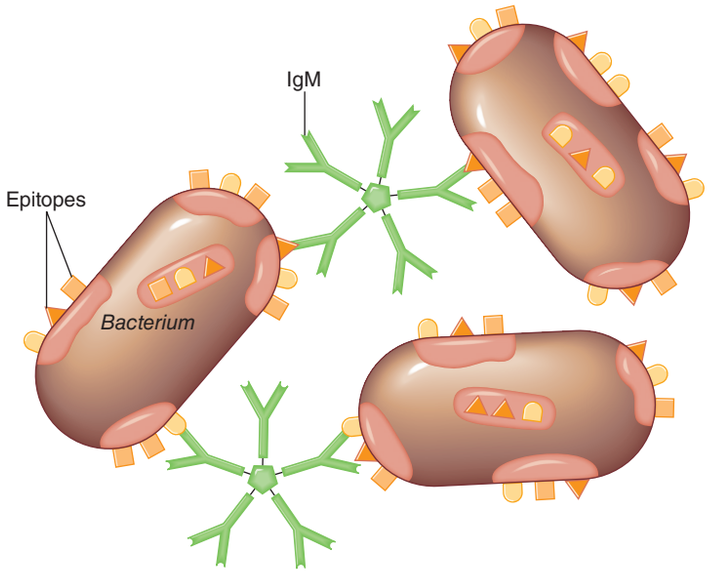


Figure 18.5 An agglutination reaction. When antibodies react with epitopes on antigens carried on neighboring cells, such as these bacteria (or red blood cells), the particulate antigens (cells) agglutinate. IgM, the most efficient immunoglobulin for agglutination, is shown here, but IgG also participates in agglutination reactions.

Q Draw an agglutination reaction involving IgG.

Other tests use electrophoresis to speed up the movement of antigen and antibody in a gel, sometimes in less than an hour, with this method. The techniques of immunodiffusion and electrophoresis can be combined in a procedure called **immunoelectrophoresis.** The procedure is used in research to separate proteins in human serum and is the basis of certain diagnostic tests. It is an essential part of the Western blot test used in AIDS testing (see Figure 10.12, page 279).

CHECK YOUR UNDERSTANDING

✓ Why does the reaction of a precipitation test become visible only in a narrow range? **18-10**

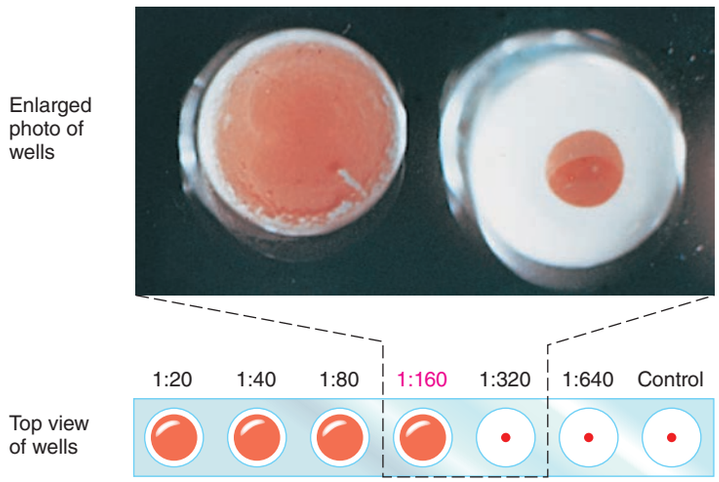
Agglutination Reactions

Whereas precipitation reactions involve *soluble* antigens, agglutination reactions involve either *particulate* antigens (particles such as cells that carry antigenic molecules) or soluble antigens adhering to particles. These antigens can be linked together by antibodies to form visible aggregates, a reaction called **agglutination** (Figure 18.5). Agglutination reactions are very sensitive, relatively easy to read (see Figure 10.10, page 278), and available in great variety. Agglutination tests are classified as either direct or indirect.

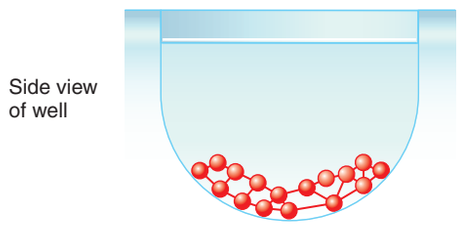
Direct Agglutination Tests

Direct agglutination tests detect antibodies against relatively large cellular antigens, such as those on red blood cells, bacteria, and fungi. They are usually done in plastic *microtiter plates,* which have many shallow wells. The amount of particulate antigen in each well is the same, but the amount of serum that contains antibodies is diluted, so that each successive well has half the antibodies of the previous well. These tests are used, for example, to test for brucellosis and to separate *Salmonella* isolates into serovars, types defined by serological means.

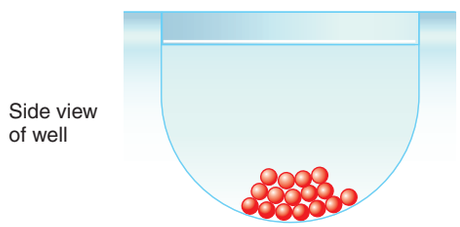
Clearly, the more antibody we start with, the more dilutions it will take to lower the amount to the point where there is not enough antibody for the antigen to react with. This is the measure of **titer,** or concentration of serum antibody (Figure 18.6).



(a) Each well in this microtiter plate contains, from left to right, only half the concentration of serum that is contained in the preceding well. Each well contains the same concentration of particulate antigens, in this instance red blood cells.



(b) Agglutinated: In a positive (agglutinated) reaction, sufficient antibodies are present in the serum to link the antigens together, forming a mat of antigen–antibody complexes on the bottom of the well.



(c) Nonagglutinated: In a negative (nonagglutinated) reaction, not enough antibodies are present to cause the linking of antigens. The particulate antigens roll down the sloping sides of the well, forming a pellet at the bottom. In this example, the antibody titer is 160 because the well with a 1:160 concentration is the most dilute concentration that produces a positive reaction.

Figure 18.6 Measuring antibody titer with the direct agglutination test.

Q What is meant by the term *antibody titer*?

For infectious diseases in general, the higher the serum antibody titer, the greater the immunity to the disease. However, the titer alone is of limited use in diagnosing an existing illness. There is no way to know whether the measured antibodies were generated in response to the immediate infection or to an earlier illness. For diagnostic purposes, *a rise in titer* is significant; that is, the titer is higher later in the course of the disease than at its outset. Also, if it can be demonstrated that the person's blood had no antibody titer before the illness but has a significant titer while the disease is progressing, this change, called **seroconversion,** is also diagnostic. This situation is frequently encountered with HIV infections.

Some diagnostic tests specifically identify IgM antibodies. Short-lived IgM is more likely to reflect a response to a current disease condition (see Chapter 17).

Indirect (Passive) Agglutination Tests

Antibodies against soluble antigens can be detected by agglutination tests if the antigens are adsorbed onto particles such as bentonite clay or, most often, minute latex beads, each about one-tenth of the diameter of a bacterium. Such tests, known as *latex agglutination tests,* are commonly used for the rapid detection of serum antibodies against many bacterial and viral diseases. In such **indirect (passive) agglutination tests,** the antibody reacts with the soluble antigen adhering to the particles (Figure 18.7). The particles then agglutinate with one another, much as particles do in the direct agglutination tests. The same principle can be applied in reverse by using particles coated with antibodies to detect the antigens against which they are specific. This approach is especially common in tests for the streptococci that cause sore throats. A diagnosis can be completed in about 10 minutes.

Hemagglutination

When agglutination reactions involve the clumping of red blood cells, the reaction is called **hemagglutination.** These reactions, which involve red blood cell surface antigens and their complementary antibodies, are used routinely in blood typing (see Table 19.2, page 522) and in the diagnosis of infectious mononucleosis.

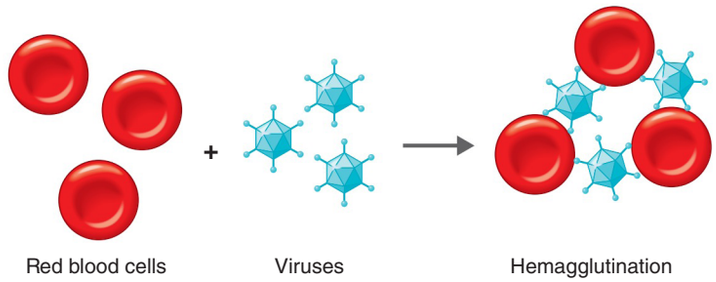


Figure 18.8 Viral hemagglutination. Viral hemagglutination is not an antigen–antibody reaction.

Q What causes agglutination in viral hemagglutination?

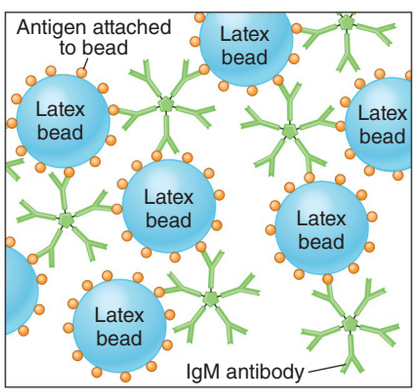
Certain viruses, such as those causing mumps, measles, and influenza, can agglutinate red blood cells without an antigen–antibody reaction; this process is called **viral hemagglutination** (Figure 18.8). This type of hemagglutination can be inhibited by antibodies that neutralize the agglutinating virus. Diagnostic tests based on such neutralization reactions are discussed in the next section.

CHECK YOUR UNDERSTANDING

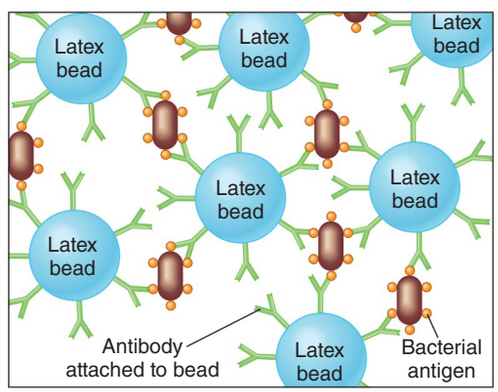
- Why wouldn't a direct agglutination test work very well with viruses? **18-11**
- Which test detects soluble antigens: agglutination or precipitation? **18-12**
- Certain diagnostic tests require red blood cells that clump visibly. What are these tests called? **18-13**

Neutralization Reactions

Neutralization is an antigen–antibody reaction in which the harmful effects of a bacterial exotoxin or a virus are blocked by antibodies. These reactions were first described in 1890, when investigators observed that immune serum could neutralize the



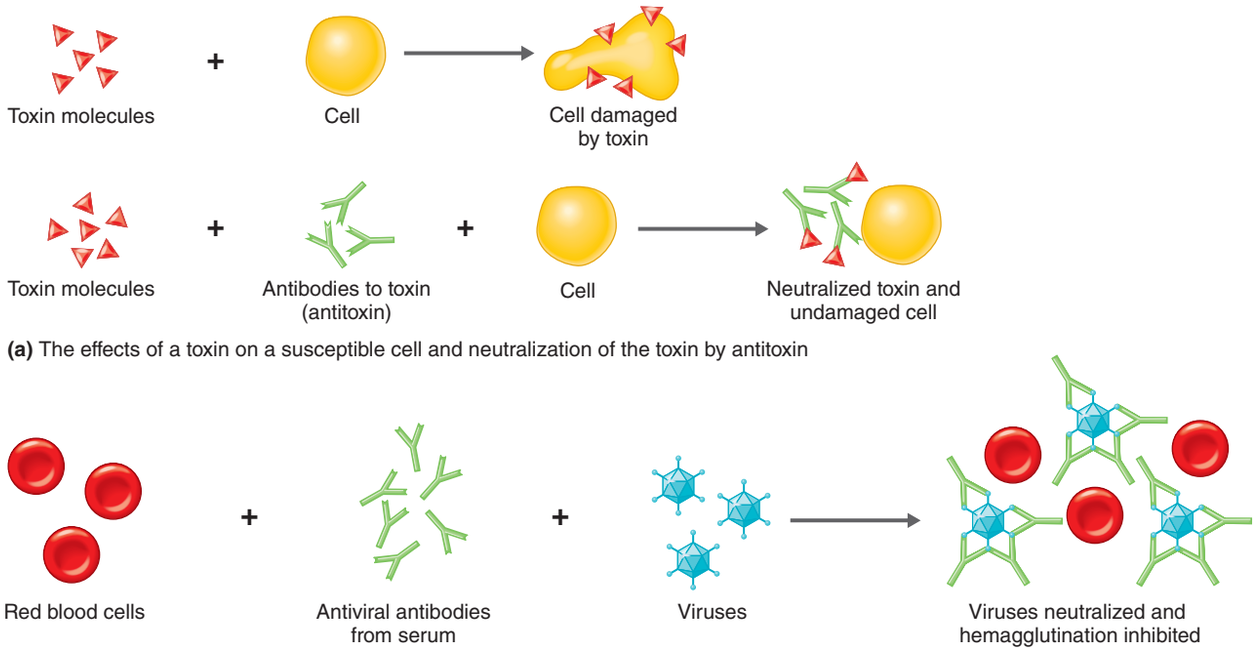
(a) Reaction in a positive indirect test for antibodies. When particles (latex beads here) are coated with antigens, agglutination indicates the presence of antibodies, such as the IgM shown here.



(b) Reaction in a positive indirect test for antigens. When particles are coated with monoclonal antibodies, agglutination indicates the presence of antigens.

Figure 18.7 Reactions in indirect agglutination tests. These tests are performed using antigens or antibodies coated onto particles such as minute latex spheres.

Q Differentiate direct from indirect agglutination tests.



(a) The effects of a toxin on a susceptible cell and neutralization of the toxin by antitoxin

(b) Viral hemagglutination test to detect antibodies to a virus. These viruses will normally cause hemagglutination when mixed with red blood cells. If antibodies to the virus are present, as shown here, they neutralize the virus and inhibit hemagglutination.

Figure 18.9 Reactions in neutralization tests.

Why does hemagglutination indicate that a patient does not have a specific disease?

toxic substances produced by the diphtheria pathogen, *Corynebacterium diphtheriae*. Such a neutralizing substance, which is called an antitoxin, is a specific antibody produced by a host as it responds to a bacterial exotoxin or its corresponding toxoid (inactivated toxin). The antitoxin combines with the exotoxin to neutralize it (Figure 18.9a). Antitoxins produced in an animal can be injected into humans to provide passive immunity against a toxin. Antitoxins from horses are routinely used to prevent or treat diphtheria and botulism; tetanus antitoxin of human origin is also used.

These therapeutic uses of neutralization reactions have led to their use as diagnostic tests. Viruses that exhibit their cytopathic (cell-damaging) effects in cell culture or embryonated eggs can be used to detect the presence of neutralizing viral antibodies (see pages 430–431). If the serum to be tested contains antibodies against the particular virus, the antibodies will prevent that virus from infecting cells in the cell culture or eggs, and no cytopathic effects will be seen. Such tests, known as in vitro neutralization tests, can thus be used both to identify a virus and to ascertain the viral antibody titer. In vitro neutralization tests are comparatively complex to carry out and are becoming less common in modern clinical laboratories.

A neutralization test used mostly for the serological typing of viruses is the **viral hemagglutination inhibition test.** Certain viruses, such as those causing influenza, mumps, and measles, have surface proteins that will cause the agglutination of red blood cells. This test is most commonly used for subtyping of influenza viruses, although more laboratories are likely to be familiar with ELISA tests for this purpose. If a person's serum contains antibodies against these viruses, these antibodies will react with the viruses and neutralize them (Figure 18.9b). For example, if hemagglutination occurs in a mixture of measles virus and red blood cells but does not occur when the patient's serum is added to the mixture, this result indicates that the serum contains antibodies that have bound to and neutralized the measles virus.

CHECK YOUR UNDERSTANDING

- In what way is there a connection between hemagglutination and certain viruses? **18-14**
- Which of these tests is an antigen–antibody reaction: precipitation or viral hemagglutination inhibition? **18-15**

Complement-Fixation Reactions

In Chapter 16 (pages 456–460), we discussed a group of serum proteins collectively called complement. During most antigen–antibody reactions, a complement serum protein binds to the antigen–antibody complex and is used up, or fixed. This process of **complement fixation** can be used to detect very small amounts of antibody. Antibodies that do not produce a visible reaction, such as precipitation or agglutination, can be demonstrated by the fixing of complement during the antigen–antibody reaction. Complement fixation was once used to diagnose syphilis (Wassermann test) and is still used to diagnose certain viral, fungal, and rickettsial diseases. The complement-fixation test requires

great care and good controls, one reason why newer, simpler tests are increasingly replacing it. The test is performed in two stages: complement fixation and indicator (Figure 18.10).

CHECK YOUR UNDERSTANDING

Why is complement given its name? **18-16**

Fluorescent-Antibody Techniques

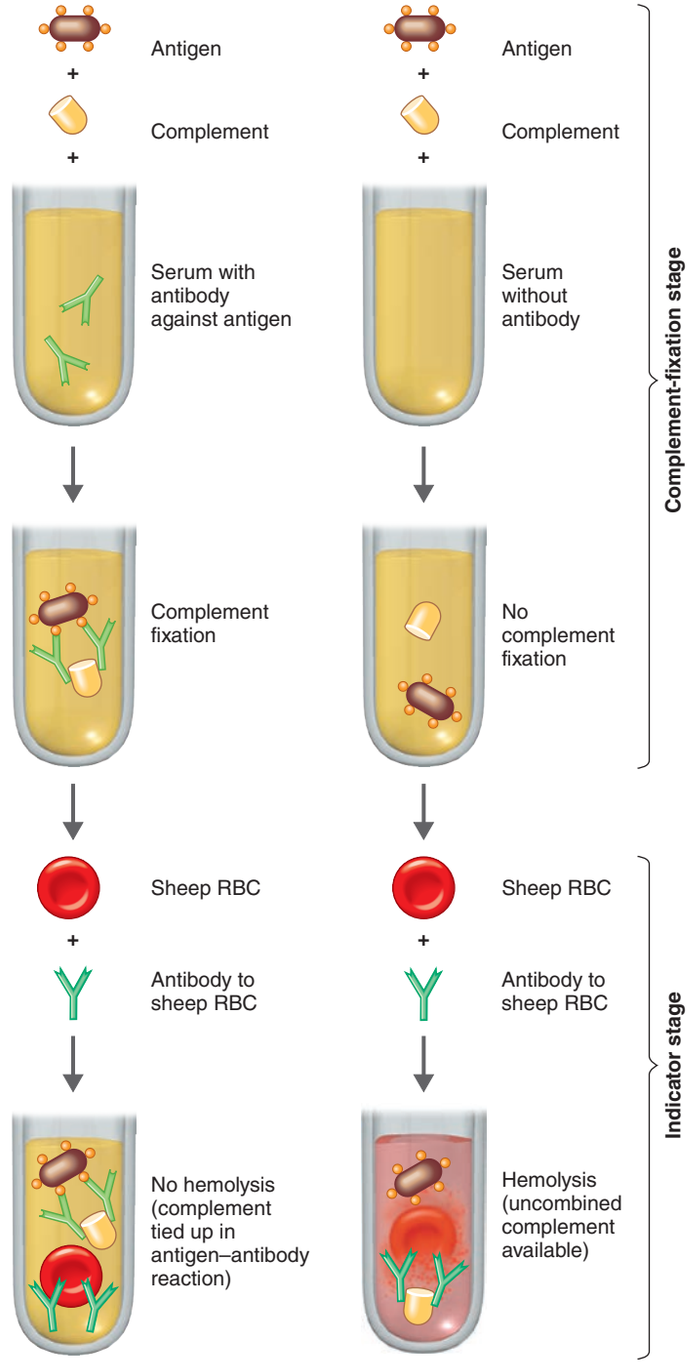
Fluorescent-antibody (FA) techniques can identify microorganisms in clinical specimens and can detect the presence of a specific antibody in serum (Figure 18.11). These techniques combine fluorescent dyes such as fluorescein isothiocyanate (FITC) with antibodies to make them fluoresce when exposed to ultraviolet light (see Figure 3.6, page 58). These procedures are quick, sensitive, and very specific; the FA test for rabies can be performed in a few hours and has an accuracy rate close to 100%.

Fluorescent-antibody tests are of two types. **Direct FA tests** are usually used to identify a microorganism in a clinical specimen (Figure 18.11a). During this procedure, the specimen containing the antigen to be identified is fixed onto a slide. Fluorescein-labeled antibodies are then added, and the slide is incubated briefly. Next, the slide is washed to remove any antibody not bound to antigen and is then examined under the fluorescence microscope for yellow-green fluorescence. The residual antibody will be visible even if the antigen, such as a virus, is submicroscopic in size.

Indirect FA tests are used to detect the presence of a specific antibody in serum following exposure to a microorganism (Figure 18.11b). They are often more sensitive than direct tests. During this procedure, a known antigen is fixed onto a slide. The test serum is then added, and, if antibody that is specific to that microbe is present, it reacts with the antigen to form a bound complex. To make the antigen–antibody complex visible, fluorescein-labeled **anti-human immune serum globulin (anti-HISG),** an antibody that reacts specifically with *any* human antibody, is added to the slide. Anti-HISG will be present only if the specific antibody has reacted with its antigen and is therefore present as well. After the slide has been incubated and washed (to remove unbound antibody), it is examined under a fluorescence microscope. If the known antigen fixed to the slide appears fluorescent, the antibody specific to the test antigen is present.

One adaptation of fluorescent antibodies is the **fluorescence-activated cell sorter (FACS).** In Chapter 17, we learned that T cells carry antigenically specific molecules such as CD4 and CD8 on their surface, and these are characteristic of certain groups of T cells. The depletion of $CD4^+$ T cells is used to follow the progression of AIDS; their populations can be determined with a FACS.

The FACS is a modification of a *flow cytometer,* in which a suspension of cells leaves a nozzle as droplets containing no more than one cell per drop (see page 279). A laser beam strikes

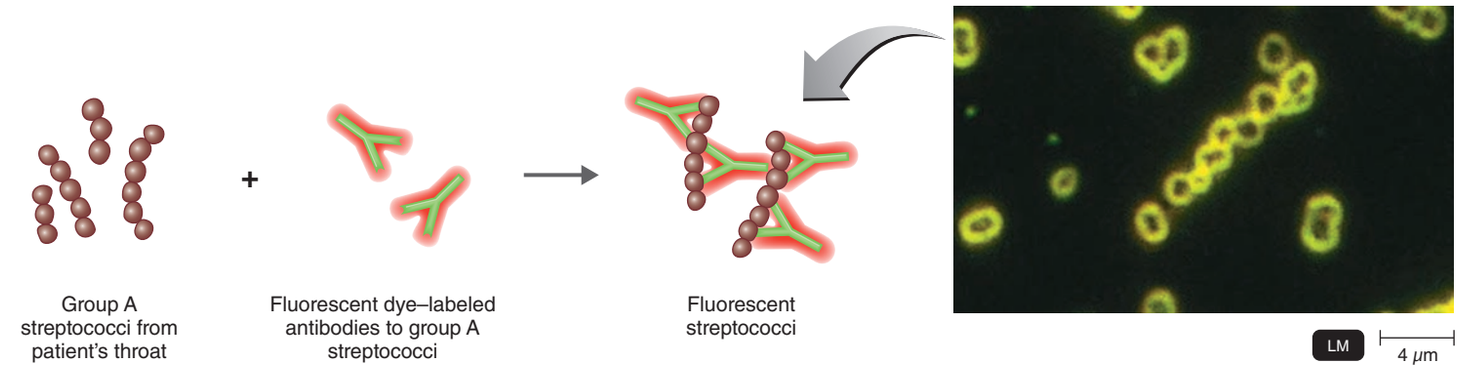


(a) Positive test. All available complement is fixed by the antigen–antibody reaction; no hemolysis occurs, so the test is positive for the presence of antibodies.

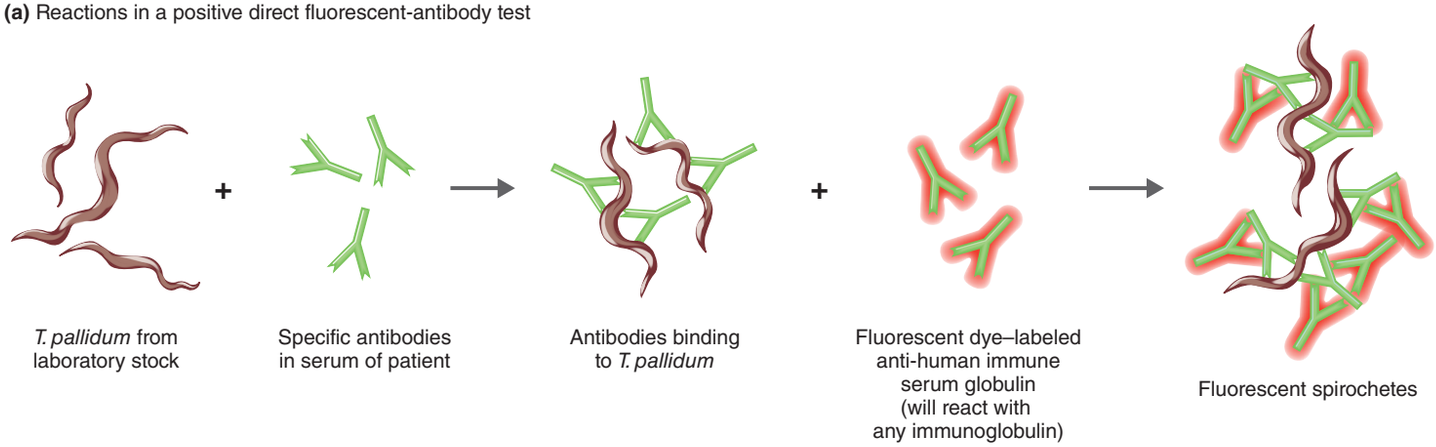
(b) Negative test. No antigen–antibody reaction occurs. The complement remains, and the red blood cells are lysed in the indicator stage, so the test is negative.

Figure 18.10 The complement-fixation test. This test indicates the presence of antibodies to a known antigen. Complement will combine (be fixed) with an antibody that is reacting with an antigen. If all the complement is fixed in the complement-fixation stage, then none remains to cause hemolysis of the red blood cells in the indicator stage.

Q Why does red blood cell lysis indicate that the patient does not have a specific disease?



(a) Reactions in a positive direct fluorescent-antibody test



(b) Reactions in a positive indirect fluorescent-antibody test

Figure 18.11 Fluorescent-antibody (FA) techniques. **(a)** A direct FA test to identify group A streptococci. **(b)** In an indirect FA test such as that used in the diagnosis of syphilis, the fluorescent dye is attached to anti-human immune serum globulin, which reacts with any human immunoglobulin (such as the *Treponema pallidum*–specific antibody) that has previously reacted with the antigen. The reaction is viewed through a fluorescence microscope, and the antigen with which the dye-tagged antibody has reacted fluoresces (glows) in the ultraviolet illumination.

Q Differentiate a direct from an indirect FA test.

each cell-containing droplet and is then received by a detector that determines certain characteristics such as size (Figure 18.12). If the cells carry FA markers to identify them as $CD4^+$ or $CD8^+$ T cells, the detector can measure this fluorescence. As the laser beam detects a cell of a preselected size or fluorescence, an electrical charge, either positive or negative, can be imparted to it. As the charged droplet falls between electrically charged plates, it is attracted to one receiving tube or another, effectively separating cells of different types. Millions of cells can be separated in an hour with this process, all under sterile conditions, which allows them to be used in experimental work.

An interesting application of the flow cytometer is sorting sperm cells to separate male (Y-carrying) and female (X-carrying) sperm. The female sperm (meaning that it will result in a female embryo when it fertilizes the egg) contains more DNA, 2.8% more in humans, 4% in animals. When the sperm is stained

Clinical Case

Data show that about half of babies with whooping cough get the illness from their parents, and an additional 25% to 35% get the infection from another household member. Neither Mr. nor Mrs. Kim has been ill, but Mark's throat is cultured for *B. pertussis,* which comes back positive. As is often the case in older children and adults, Mark's symptoms are milder than his infant sister's; infants with whooping cough can become severely ill and die.

Why is vaccination against pertussis so important?

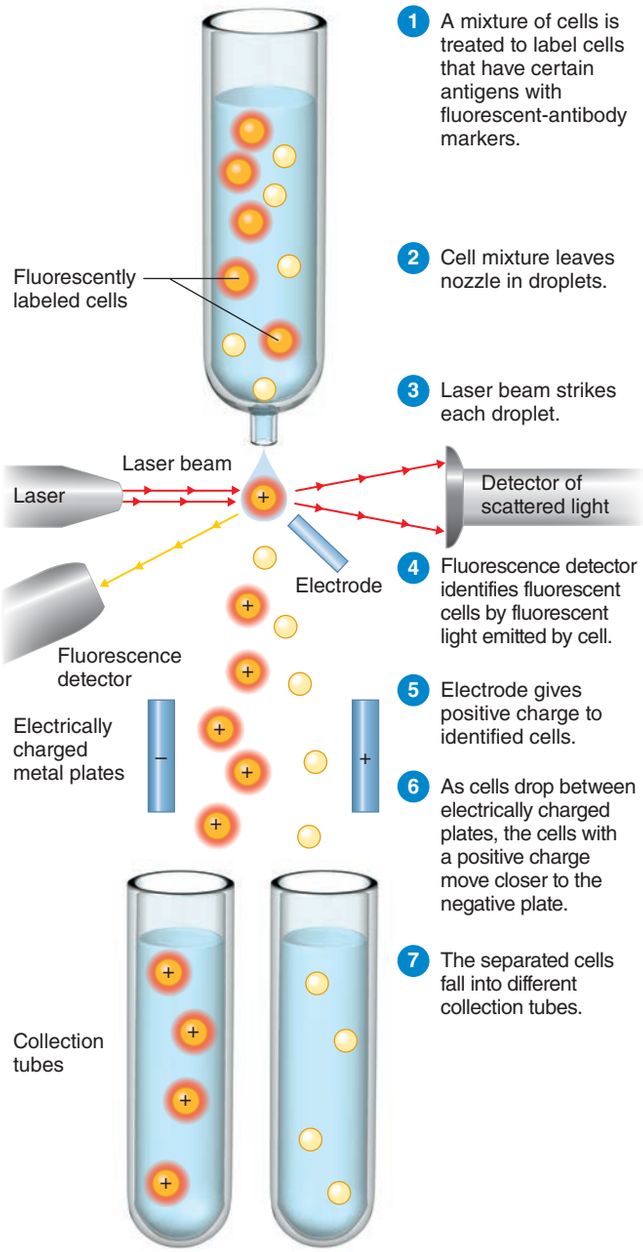


Figure 18.12 The fluorescence-activated cell sorter (FACS). This technique can be used to separate different classes of T cells. For example, a fluorescence-labeled antibody reacts with, for example, the CD4 molecule on a T cell.

Q Provide an application of FACS to follow the progress of HIV infection.

with a fluorescent dye specific for DNA, the female sperm glows more brightly when illuminated by the laser beam because it has more DNA and therefore can be separated out. The technique was developed for agricultural purposes. However, it has received medical approval for use in human couples who carry genes for inherited diseases that affect only boys.

CHECK YOUR UNDERSTANDING

Which test is used to detect antibodies against a pathogen: the direct or the indirect fluorescent-antibody test? **18-17**

Enzyme-Linked Immunosorbent Assay (ELISA)

The **enzyme-linked immunosorbent assay (ELISA)** is the most widely used of a group of tests known as *enzyme immunoassay (EIA)*. There are two basic methods. The *direct ELISA* detects antigens, and the *indirect ELISA* detects antibodies. A microtiter plate with numerous shallow wells is used in both procedures (see Figure 10.11a, page 278). Variations of the test exist; for example, the reagents can be bound to tiny latex particles rather than to the surfaces of the microtiter plates. ELISA procedures are popular primarily because they require little interpretive skill to read; the results tend to be clearly positive or clearly negative.

Many ELISA tests are available for clinical use in the form of commercially prepared kits. Procedures are often highly automated, with the results read by a scanner and printed out by computer. Some tests based on this principle are also available for use by the public, including a commonly available home pregnancy test (**Figure 18.13**).

Direct ELISA

The direct ELISA method is shown in **Figure 18.14a** (page 510). A common use of the direct ELISA test is to detect the presence of drugs in urine. For these tests, antibodies specific for the drug are adsorbed to a well of the microtiter plate. (The availability of monoclonal antibodies has been essential to the widespread use of the ELISA test.) When the patient's urine sample is added to the well, any of the drug that it contained would bind to the antibody and is captured. The well is rinsed to remove any unbound drug. To make a visible test, more antibodies specific to the drug are now added (these antibodies have an enzyme attached to them—therefore, the term *enzyme-linked*) and will react with the already-captured drug, forming a "sandwich" of antibody/drug/enzyme-linked antibody. This positive test can be detected by adding a substrate for the linked enzyme; a visible color is produced by the enzyme reacting with its substrate.

Indirect ELISA

The indirect ELISA test, illustrated in Figure 18.14b, detects antibodies in a patient's sample rather than an antigen such as a drug. Indirect ELISA tests are used, for example, to screen blood for antibodies to HIV (see page 540). For such a purpose, the microtiter wells contain antigens, such as the inactivated virus that causes the disease the test is designed to diagnose. A sample of the patient's blood is added to the well; if it contains antibodies against the virus, they will react. The well is rinsed to remove unbound antibodies. If antibodies in the blood

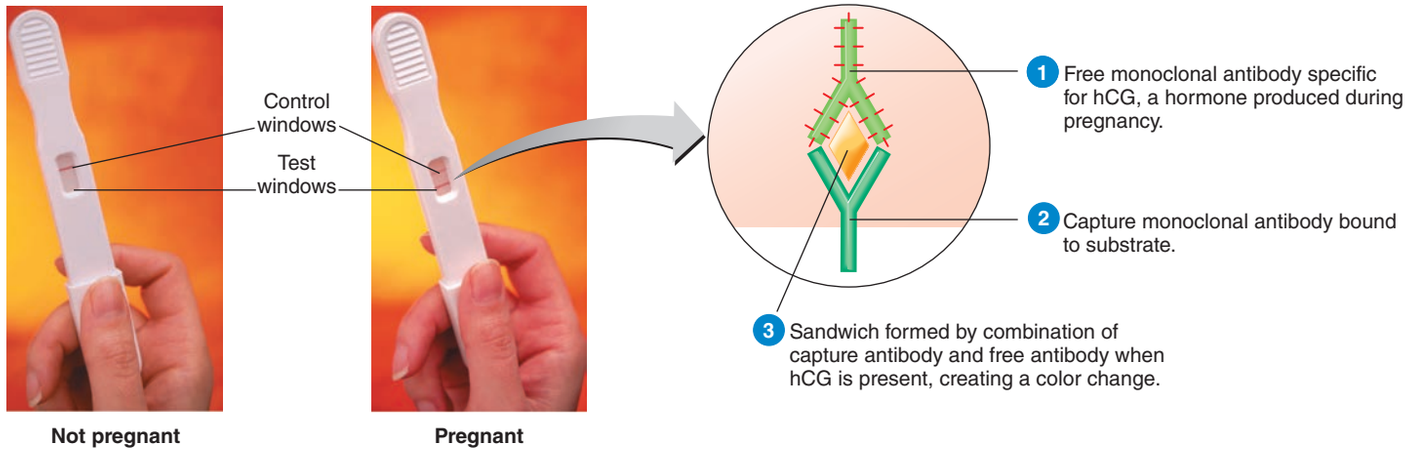
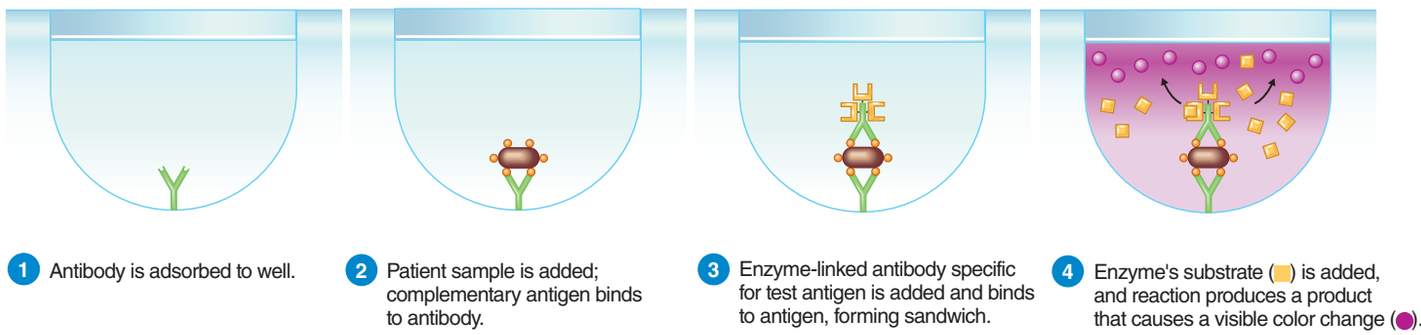


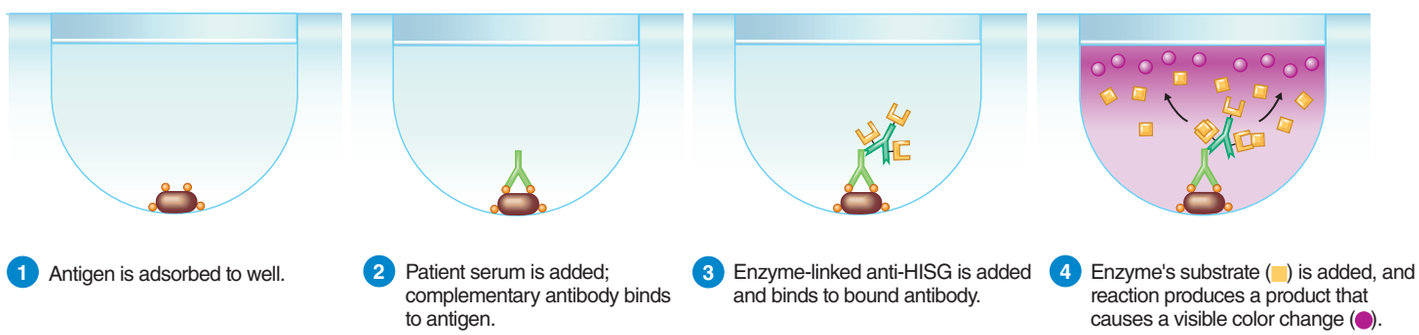
Figure 18.13 The use of monoclonal antibodies in a home pregnancy test. Home pregnancy tests detect a hormone called human chorionic gonadotropin (hCG) that is excreted only in the urine of a pregnant woman.

Q What is the antigen in the home pregnancy test?

and the virus in the well have attached to each other, they will remain in the well—a positive test. To make a positive test visible, some anti-HISG (an immunoglobulin that will attach to *any* antibody, including the one in the patient's serum that has attached to the virus in the well; see page 507) is added. The anti-HISG is linked to an enzyme. A positive test consists of a "sandwich" of a virus/antibody/enzyme-linked-anti-HISG. At this point, the substrate for the enzyme is added, and a positive test is detected by the color change caused by the enzyme linked to the anti-HISG.



(a) A positive **direct** ELISA to detect antigens



(b) A positive **indirect** ELISA to detect antibodies

Figure 18.14 The ELISA method. The components are usually contained in small wells of a microtiter plate. For an illustration of a technician carrying out an ELISA test on such a microtiter plate and the use of a computer to read the results, see Figure 10.11 on page 278.

Q Differentiate a direct from an indirect ELISA test.

Western Blotting (Immunoblotting)

Western blotting, often simply called *immunoblotting,* can identify a specific protein in a mixture. When this specific protein is an antibody, the technique is valuable in diagnosing disease. The components of the mixture are separated by electrophoresis in a gel and then transferred to a protein-binding sheet (blotter). There the blot is flooded with an enzyme-linked antibody. The location of the antigen and the enzyme-linked antibody reactant can be visualized, usually with a color-reacting label similar to an ELISA test reaction (see Figure 18.14). The most frequent application is in a confirmatory test for HIV infection (see page 540). Figure 10.12 on page 279 illustrates the procedure.*

CHECK YOUR UNDERSTANDING

- Which test is used to detect antibodies against a pathogen: the direct or the indirect ELISA test? **18-18**
- How are antibodies detected in Western blotting? **18-19**

The Future of Diagnostic and Therapeutic Immunology

The introduction of monoclonal antibodies has revolutionized diagnostic immunology by making available large, economical amounts of specific antibodies. This has led to many newer diagnostic tests that are more sensitive, specific, rapid, and simpler to use. For example, tests to diagnose sexually transmitted chlamydial infections and certain protozoan-caused intestinal parasitic diseases are coming into common use. These tests had previously required relatively difficult culture or microscopic methods for diagnosis. At the same time, the use of many of the classic serological tests, such as complement-fixation tests, is declining. Most newer tests will require less human judgment to read, and they require fewer highly trained personnel.

The use of certain *nonimmunological* tests, such as polymerase chain reaction (PCR) and DNA probes that were discussed in Chapter 10 (page 281), is increasing. Some of these tests will become automated to a significant degree. For example, a DNA chip (see Figure 10.17, page 283) containing over 50,000 DNA probes for genetic information expected in possible pathogens can be exposed to a test sample. This chip is scanned and its data automatically analyzed. PCR tests are also becoming highly automated.

Most of the diagnostic tests described in this chapter are those used in the developed world, where laboratory budgets are lavish compared to the funds available in the developing world. In many countries the money available for diagnosis and treatment alike is tragically small.

*The naming of Western blotting is a bit of scientific whimsy. The Southern blotting procedure used for detecting DNA fragments (page 281), which was named for the inventor Ed Southern, led to a similar procedure for detecting mRNA fragments that was named Northern blotting. This "directional system" was continued when a new blotting procedure for identifying proteins was developed—hence, Western blotting.

Clinical Case Resolved

Among the diseases for which universal childhood vaccination is recommended in the United States, only pertussis has increased in incidence during the past 20 years. Adults and adolescents might be a community reservoir for *B. pertussis* because immunity from childhood vaccination declines beginning 5 to 15 years after the last pertussis vaccine dose.

The public's sense of the importance of childhood vaccinations has also declined; consequently, many children are not fully immunized. The CDC now recommends that adults get revaccinated with a combination vaccine that prevents tetanus, diphtheria, and pertussis.

493 497 500 503 508 511

The diseases that most of these diagnostic methods target are also those that are more likely to be found in developed countries. In many parts of the world, especially tropical Africa and tropical Asia, there is an urgent need for diagnostic tests for diseases endemic in those areas, such as malaria, leishmaniasis, AIDS, Chagas' disease, and tuberculosis. These tests will need to be inexpensive and simple enough to be carried out by personnel with minimal training.

The tests described in this chapter are most often used to detect existing disease. In the future, diagnostic testing will probably also be directed at *preventing* disease. In the United States we regularly see reports of outbreaks of foodborne disease. Fresh produce does not carry the identifying marks that facilitate the tracking of packaged food products. Thus, sampling methods that would allow complete identification (including specific pathogenic serovars) within a few hours, or even minutes, would save valuable time in tracking outbreaks of infectious disease carried by fruits and vegetables. This saving in time would be translated into immense economic savings for growers and retailers. It would also lead to less human illness and, perhaps, save lives.

Not every topic discussed in this chapter is necessarily directed at detecting and preventing disease. As was mentioned on page 501, Mabs have applications in the therapy of disease as well. These are already in use to treat certain cancers such as breast cancer and non-Hodgkin's lymphoma, as well as inflammatory diseases such as rheumatoid arthritis. Currently, Mabs are being tested for many disease conditions; these include asthma, sepsis, coronary artery disease, and several viral infections. They are also being studied as a way to treat multiple sclerosis, an immune-caused neurological disease.

CHECK YOUR UNDERSTANDING

- How has the development of monoclonal antibodies revolutionized diagnostic immunology? **18-20**

Study Outline

MasteringMicrobiology®
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Check out the Study Area of MasteringMicrobiology to explore Interactive Microbiology. Study on-the-go with Dynamic Study Modules. Check your understanding with chapter quizzes and animations—and much more!

Vaccines (pp. 493–500)

1. Edward Jenner developed the modern practice of vaccination when he inoculated people with cowpox virus to protect them against smallpox.

Principles and Effects of Vaccination (pp. 493–495)

2. Herd immunity results when most of a population is immune to a disease.

Types of Vaccines and Their Characteristics (pp. 495–497)

3. Live attenuated vaccines consist of attenuated (weakened) microorganisms; attenuated virus vaccines generally provide lifelong immunity.
4. Inactivated vaccines consist of killed bacteria or viruses.
5. Subunit vaccines consist of antigenic fragments of a microorganism; these include recombinant vaccines and toxoids.
6. Conjugated vaccines combine the desired antigen with a protein that boosts the immune response.
7. Nucleic acid (DNA) vaccines cause the recipient to make the antigenic protein.

The Development of New Vaccines (pp. 497–498)

8. Viruses for vaccines may be grown in animals, cell cultures, or chick embryos.
9. Recombinant vaccines and nucleic acid vaccines do not need to be grown in cells or animals.
10. Genetically modified plants may someday provide edible vaccines.

Vaccination Technologies (p. 498)

11. Combining several vaccines would eliminate the number of injections.
12. Dry skin patch vaccines don't need refrigeration.

Adjuvants (pp. 499–500)

13. Adjuvants improve the effectiveness of some antigens.

Safety of Vaccines (p. 500)

14. Vaccines are the safest and most effective means of controlling infectious diseases.

Diagnostic Immunology (pp. 500–511)

Immunologic-Based Diagnostic Tests (pp. 500–501)

1. Many tests based on the interactions of antibodies and antigens have been developed to determine the presence of antibodies or antigens in a patient.
2. The sensitivity of a diagnostic test is determined by the percentage of positive samples it correctly detects; and its specificity is determined by the percentage of false positive results it gives.

Monoclonal Antibodies (pp. 501–503)

3. Hybridomas are produced in the laboratory by fusing a cancerous cell with an antibody-secreting plasma cell.
4. A hybridoma cell culture produces large quantities of the plasma cell's antibodies, called monoclonal antibodies.
5. Monoclonal antibodies are used in serological identification tests, to prevent tissue rejections, and to make immunotoxins to treat cancer.

Precipitation Reactions (pp. 503–504)

6. The interaction of soluble antigens with IgG or IgM antibodies leads to precipitation reactions.
7. Precipitation reactions depend on the formation of lattices and occur best when antigen and antibody are present in optimal proportions. Excesses of either component decrease lattice formation and subsequent precipitation.
8. Immunodiffusion procedures are precipitation reactions carried out in an agar gel medium.
9. Immunoelectrophoresis combines electrophoresis with immunodiffusion for the analysis of serum proteins.

Agglutination Reactions (pp. 504–505)

10. The interaction of particulate antigens (cells that carry antigens) with antibodies leads to agglutination reactions.
11. Diseases may be diagnosed by combining the patient's serum with a known antigen.
12. Diseases can be diagnosed by a rising titer or seroconversion (from no antibodies to the presence of antibodies).
13. Direct agglutination reactions can be used to determine antibody titer.
14. Antibodies cause visible agglutination of soluble antigens affixed to latex spheres in indirect or passive agglutination tests.
15. Hemagglutination reactions involve agglutination reactions using red blood cells. Hemagglutination reactions are used in blood typing, the diagnosis of certain diseases, and the identification of viruses.

Neutralization Reactions (pp. 505–506)

16. In neutralization reactions, the harmful effects of a bacterial exotoxin or virus are eliminated by a specific antibody.
17. An antitoxin is an antibody produced in response to a bacterial exotoxin or a toxoid that neutralizes the exotoxin.
18. In a virus neutralization test, the presence of antibodies against a virus can be detected by the antibodies' ability to prevent cytopathic effects of viruses in cell cultures.
19. Antibodies against certain viruses can be detected by their ability to interfere with viral hemagglutination in viral hemagglutination inhibition tests.

Complement-Fixation Reactions (pp. 506–507)

20. Complement-fixation reactions are serological tests based on the depletion of a fixed amount of complement in the presence of an antigen–antibody reaction.

Fluorescent-Antibody Techniques (pp. 507–509)

21. Fluorescent-antibody techniques use antibodies labeled with fluorescent dyes.

22. Direct fluorescent-antibody tests are used to identify specific microorganisms.
23. Indirect fluorescent-antibody tests are used to demonstrate the presence of antibody in serum.
24. A fluorescence-activated cell sorter can be used to detect and count cells labeled with fluorescent antibodies.

Enzyme-Linked Immunosorbent Assay (ELISA) (pp. 509–510)

25. ELISA techniques use antibodies linked to an enzyme.
26. Antigen–antibody reactions are detected by enzyme activity. If the indicator enzyme is present in the test well, an antigen–antibody reaction has occurred.
27. The direct ELISA is used to detect antigens against a specific antibody bound in a test well.
28. The indirect ELISA is used to detect antibodies against an antigen bound in a test well.

Western Blotting (Immunoblotting) (p. 511)

29. Serum antibodies separated by electrophoresis are identified with an enzyme-linked antibody.

The Future of Diagnostic and Therapeutic Immunology (p. 511)

30. The use of monoclonal antibodies will continue to make new diagnostic tests possible.

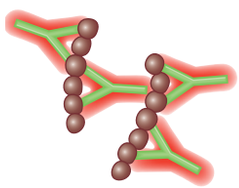
Study Questions

For Answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

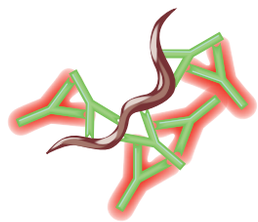
Knowledge and Comprehension

Review

1. Classify the following vaccines by type. Which could cause the disease it is supposed to prevent?
   - **a.** attenuated measles virus
   - **b.** dead *Rickettsia prowazekii*
   - **c.** *Vibrio cholerae* toxoid
   - **d.** hepatitis B antigen produced in yeast cells
   - **e.** purified polysaccharides from *Streptococcus pyogenes*
   - **f.** *Haemophilus influenzae* polysaccharide bound to diphtheria toxoid
   - **g.** a plasmid containing genes for influenza A protein
2. Define the following terms, and give an example of how each reaction is used diagnostically:
   - **a.** viral hemagglutination
   - **b.** hemagglutination inhibition
   - **c.** passive agglutination
3. DRAW IT Label the components of the direct and indirect FA tests in the following situations. Which test is direct? Which test provides definitive proof of disease?

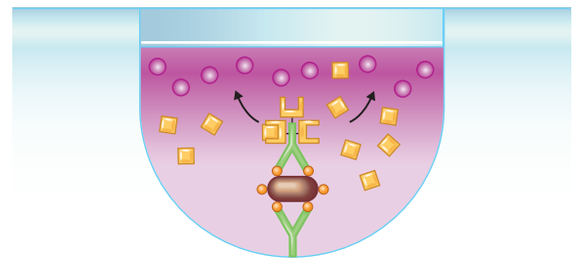


(a) Rabies can be diagnosed postmortem by mixing fluorescent-labeled antibodies with brain tissue.

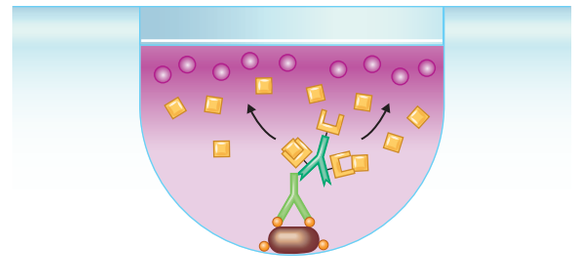


(b) Syphilis can be diagnosed by adding the patient's serum to a slide fixed with *Treponema pallidum*. Anti-human immune serum globulin tagged with a fluorescent dye is added.

4. How are monoclonal antibodies produced? What is their advantage over horse serum?
5. Explain the effects of excess antigen and antibody on the precipitation reaction. How is the precipitin ring test different from an immunodiffusion test?
6. DRAW IT Label components of the direct and indirect ELISA tests in the situations shown below. Which test is direct? Which test provides definitive proof of disease?



(a) Respiratory secretions to detect respiratory syncytial virus



(b) Blood to detect human immunodeficiency virus antibodies

7. How does the antigen in an agglutination reaction differ from that in a precipitation reaction?
8. Match the following serological tests in column A to the descriptions in column B.

Column A	Column B
_____ a. Precipitation	1. Occurs with particulate antigens
_____ b. Western blotting	2. Uses an enzyme for the indicator
_____ c. Agglutination	3. Uses red blood cells for the indicator
_____ d. Complement fixation	4. Uses antihuman immune serum globulin
_____ e. Neutralization	5. Occurs with a free soluble antigen
_____ f. ELISA	6. Used to determine the presence of antitoxin

9. Match each of the following tests in column A to its positive reaction in column B.

Column A	Column B
_____ a. Agglutination	1. Peroxidase activity
_____ b. Complement fixation	2. Harmful effects of agents not seen
_____ c. ELISA	3. No hemolysis
_____ d. FA test	4. Cloudy white line
_____ e. Neutralization	5. Cell clumping
_____ f. Precipitation	6. Fluorescence

10. NAME IT A purified protein from *Mycobacterium tuberculosis* is injected into a person's skin. A hardened, red area develops around the injection site within 3 days.

Multiple Choice

Use the following choices to answer questions 1 and 2:

a. hemolysis
b. hemagglutination
c. hemagglutination inhibition
d. no hemolysis
e. precipitin ring forms

1. Patient's serum, influenza virus, sheep red blood cells, and anti-sheep red blood cells are mixed in a tube. What happens if the patient has antibodies against influenza?

2. Patient's serum, *Chlamydia,* guinea pig complement, sheep red blood cells, and anti-sheep red blood cells are mixed in a tube. What happens if the patient has antibodies against *Chlamydia*?

3. The examples in questions 1 and 2 are
a. direct tests.
b. indirect tests.

Use the following choices to answer questions 4 and 5:

a. anti-*Brucella*
b. *Brucella*
c. substrate for the enzyme

4. Which is the third step in a direct ELISA test?

5. Which item is from the patient in an indirect ELISA test?

6. In an immunodiffusion test, a strip of filter paper containing diphtheria antitoxin is placed on a solid culture medium. Then bacteria are streaked perpendicular to the filter paper. If the bacteria are toxigenic,
a. the filter paper will turn red.
b. a line of antigen–antibody precipitate will form.
c. the cells will lyse.
d. the cells will fluoresce.
e. none of the above

Use the following choices to answer questions 7–9.

a. direct fluorescent antibody
b. indirect fluorescent antibody
c. rabies immune globulin
d. killed rabies virus
e. none of the above

7. Treatment given to a person bitten by a rabid bat.

8. Test used to identify rabies virus in the brain of a dog.

9. Test used to detect the presence of antibodies in a patient's serum.

10. In an agglutination test, eight serial dilutions to determine antibody titer were set up: Tube 1 contained a 1:2 dilution; tube 2, a 1:4, and so on. If tube 5 is the last tube showing agglutination, what is the antibody titer?
a. 5 **b.** 1:5 **c.** 32 **d.** 1:32

Analysis

1. What problems are associated with the use of live attenuated vaccines?

2. Many of the serological tests require a supply of antibodies against pathogens. For example, to test for *Salmonella,* anti-*Salmonella* antibodies are mixed with the unknown bacterium. How are these antibodies obtained?

3. A test for antibodies against *Treponema pallidum* uses the antigen cardiolipin and the patient's serum (suspected of having antibodies). Why do the antibodies react with cardiolipin? What is the disease?

Clinical Applications and Evaluation

1. Which of the following is proof of a disease state? Why doesn't the other situation confirm a disease state? What is the disease?
a. *Mycobacterium tuberculosis* is isolated from a patient.
b. Antibodies against *M. tuberculosis* are found in a patient.

2. Streptococcal erythrogenic toxin is injected into a person's skin in the Dick test. What results are expected if a person has antibodies against this toxin? What type of immunological reaction is this? What is the disease?

3. The following data were obtained from FA tests for anti-*Legionella* in four people. What conclusions can you draw? What is the disease?

	Antibody Titer			
	Day 1	**Day 7**	**Day 14**	**Day 21**
Patient A	128	256	512	1024
Patient B	0	0	0	0
Patient C	256	256	256	256
Patient D	0	0	128	512

4. Maria decided against the relatively new chickenpox vaccine and used her parents' method: she wanted her children to get chickenpox so that they would develop natural immunity. Her two children did get chickenpox. Her son had slight itching and skin vesicles, but her daughter was hospitalized for months with streptococcal cellulitis and underwent several skin grafts before recovering. Maria's housekeeper contracted chickenpox from the children and subsequently died. Almost half of the deaths due to chickenpox occur in adults.
a. What responsibilities do parents have for their children's health?
b. What rights do individuals have? Should vaccination be required by law?
c. What responsibilities do individuals (e.g., parents) have for the health of society?
d. Vaccines are given to healthy people, so what risks are acceptable?



In the Clinic

As an AIDS nurse, you discuss the HIV status of a newborn with Jessica, her HIV-positive mother. The infant tested positive by ELISA and Western blot, but the PCR test was negative for HIV. **Does the infant have HIV infection? How do you explain the seemingly conflicting test results to Jessica? And what advice do you give the Jessica to prevent transmitting HIV to her baby?**

Hint: Read about diagnostic methods for HIV (on pages 540–541).

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

19 Disorders Associated with the Immune System

Normally cells of the immune system remove or neutralize injurious agents, like the two lymphocytes shown attacking a cancer cell in the photograph. However, in this chapter we see that not all immune system responses produce a desirable result. A familiar example is hay fever, which results from repeated exposure to plant pollen. Most of us also know that a blood transfusion will be rejected if the blood of the donor and the blood of the recipient are not compatible and that rejection is also a potential problem with transplanted organs. One's own tissue may be mistakenly attacked by the immune system, causing diseases we classify as autoimmune. Certain antigens, called superantigens, indiscriminately activate many T-cell receptors at once, causing a cytokine storm that results in damage to tissue.

Some people are born with a defective immune system (see the Clinical Case in this chapter), and in all of us the effectiveness of our immune system declines with age. Our immune systems can be deliberately crippled (*immunosuppressed*) to prevent the rejection of transplanted organs. Disease can also impair the immune system, especially infection by HIV, a virus that specifically attacks the immune system.

Two lymphocytes (yellow) attacking a cancer cell.

Hypersensitivity

LEARNING OBJECTIVES

- **19-1** Define *hypersensitivity*.
- **19-2** Describe the mechanism of anaphylaxis.
- **19-3** Compare and contrast systemic and localized anaphylaxis.
- **19-4** Explain how allergy skin tests work.
- **19-5** Define *desensitization* and *blocking antibody*.
- **19-6** Describe the mechanism of cytotoxic reactions and how drugs can induce them.
- **19-7** Describe the basis of the ABO and Rh blood group systems.
- **19-8** Explain the relationships among blood groups, blood, transfusions, and hemolytic disease of the newborn.
- **19-9** Describe the mechanism of immune complex reactions.
- **19-10** Describe the mechanism of delayed cell-mediated reactions, and name two examples.

The term **hypersensitivity** refers to an antigenic response beyond that which is considered normal; allergies are a familiar example. Hypersensitivity responses occur in individuals who have been *sensitized* by previous exposure to an antigen, which in this context is sometimes called an **allergen.** When an individual who was previously sensitized is exposed to that antigen again, his or her immune system reacts to it in a damaging manner. The four principal types of hypersensitivity reactions, summarized in Table 19.1, are anaphylactic, cytotoxic, immune complex, and cell-mediated (or delayed-type) reactions.

Allergies and the Microbiome

The incidence of food and environmental allergies is increasing in developed nations. The *hygiene hypothesis* suggests that limiting childhood exposure to bacteria and parasites may lower immune tolerance and the body's ability to cope with harmless antigens, such as food or pollen. The resident microbiota within the human body is also being studied as a factor in certain autoimmune diseases. For more on this, see the **Big Picture** feature on the human microbiome on pages 518–519.

CHECK YOUR UNDERSTANDING

✓ Are all immune responses beneficial? **19-1**

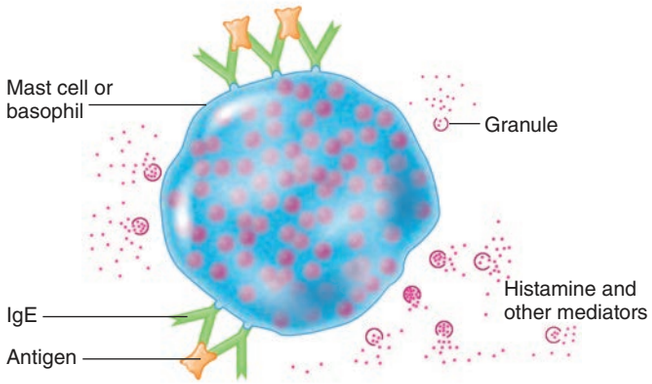
Type I (Anaphylactic) Reactions

Type I, or anaphylactic, reactions often occur within 2 to 30 minutes after a person sensitized to an antigen is reexposed to that antigen. *Anaphylaxis* means "the opposite of protected," from the prefix *ana-*, meaning against, and the Greek *phylaxis,* meaning protection. **Anaphylaxis** is an inclusive term for the reactions caused when certain antigens combine with IgE antibodies. Anaphylactic responses can be *systemic reactions*, which produce shock and breathing difficulties and are sometimes fatal, or *localized reactions,* which include common allergic conditions such as hay fever, asthma, and hives (slightly raised, often itchy and reddened areas of the skin).

The IgE antibodies produced in response to an antigen, such as insect venom or plant pollen, bind to the surfaces of cells such as mast cells and basophils. These two cell types are similar in morphology and in their contribution to allergic reactions. **Mast cells** are especially prevalent in the mucosal and connective tissue of the skin and respiratory tract and in surrounding blood vessels. The name is from the German word *mastzellen,* meaning well fed; they are packed with granules that at one time were mistakenly thought to have been ingested (Figure 19.1a). **Basophils** recruited to the site of an infection circulate in the bloodstream, where they constitute fewer than 1% of the leukocytes. Both cell types are filled with granules containing a variety of chemicals called *mediators.*

TABLE 19.1 Types of Hypersensitivity

Type of Reaction	Time Before Clinical Signs	Characteristics	Examples
Type I (Anaphylactic)	<30 min	IgE binds to mast cells or basophils; causes degranulation of mast cell or basophil and release of reactive substances such as histamine.	Anaphylactic shock from drug injections and insect venom; common allergic conditions, such as hay fever, asthma
Type II (Cytotoxic)	5–12 hours	Antigen causes formation of IgM and IgG antibodies that bind to target cell; when combined with action of complement, destroys target cell.	Transfusion reactions, Rh incompatibility
Type III (Immune Complex)	3–8 hours	Antibodies and antigens form complexes that cause damaging inflammation.	Arthus reactions, serum sickness
Type IV (Delayed Cell-Mediated, or Delayed Hypersensitivity)	24–48 hours	Antigens activate T_C that kills target cell.	Rejection of transplanted tissues; contact dermatitis, such as poison ivy; certain chronic diseases, such as tuberculosis



(a) IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.



(b) A degranulated mast cell that has reacted with an antigen and released granules of histamine and other reactive mediators

Figure 19.1 The mechanism of anaphylaxis.

Q What type of cells do IgE antibodies bind to?

Mast cells and basophils can have as many as 500,000 sites for IgE attachment. The Fc (stem) region of an IgE antibody (see Figure 17.4, page 473) can attach to one of these specific receptor sites on such a cell, leaving two antigen-binding sites free. Of course, the attached IgE monomers will not all be specific for the same antigen. But when an antigen such as plant pollen encounters two adjacent antibodies of the same appropriate specificity, it can bind to one antigen-binding site on each antibody, bridging the space between them. This bridge triggers the mast cell or basophil to undergo **degranulation,** which releases the granules inside these cells and also the mediators they contain (Figure 19.1b).

These mediators cause the unpleasant and damaging effects of an allergic reaction. The best-known mediator is **histamine.** The release of histamine increases the permeability and distension of blood capillaries, resulting in edema (swelling) and erythema (redness). Other effects include increased mucus secretion (a runny nose, for example) and smooth muscle contraction, which in the respiratory bronchi results in breathing difficulty.

Other mediators include **leukotrienes** of various types and **prostaglandins.** These mediators are not preformed and stored in the granules but are synthesized by the antigen-triggered cell. Because leukotrienes tend to cause prolonged contractions of certain smooth muscles, their action contributes to the spasms of the bronchial tubes that occur during asthmatic attacks. Prostaglandins affect smooth muscles of the respiratory system and increase mucus secretion.

Collectively, all these mediators serve as chemotactic agents that, in a few hours, attract neutrophils and eosinophils to the site of the degranulated cell.

Systemic Anaphylaxis

At the turn of the twentieth century, two French biologists studied the responses of dogs to the venom of stinging jellyfish. Large doses of venom usually killed the dogs, but sometimes a few survived the injections. These surviving dogs were used for repeat experiments with the venom, and the results were surprising. Even a very tiny dose of the venom, one that should have been almost harmless, killed the dogs. They suffered difficulty in respiration, entered shock as their cardiovascular systems collapsed, and quickly died. This phenomenon was called *anaphylactic shock.*

Systemic anaphylaxis (or *anaphylactic shock*) can result when an individual sensitized to an antigen is exposed to it again. Even a small dose of the antigen in question may cause a systemic reaction in someone who is sensitized to it. Injected antigens are more likely to cause a dramatic response than

Clinical Case: Who Are You?

Malik, a 10-day-old infant, has just been brought home from the neonatal intensive care unit (NICU) after heart surgery to repair a heart defect. When his mother is changing his diaper, she notices a rash on his buttocks. Assuming diaper rash, Malik's mother treats the area with diaper rash ointment and thinks nothing else of it. As the day progresses, the rash spreads to Malik's face, giving him the appearance of being slapped. By the time Malik's parents bring him to the emergency department (ED), the rash is lobster-red and has spread to his entire body.

What is causing Malik's rash? Read on to find out.

517 521 531 534 544

BIG PICTURE

Human Microbiome and IBD

The Human Microbiome Project uses genetic sequencing to study correlations between changes in the microbiome and inflammatory bowel disease.

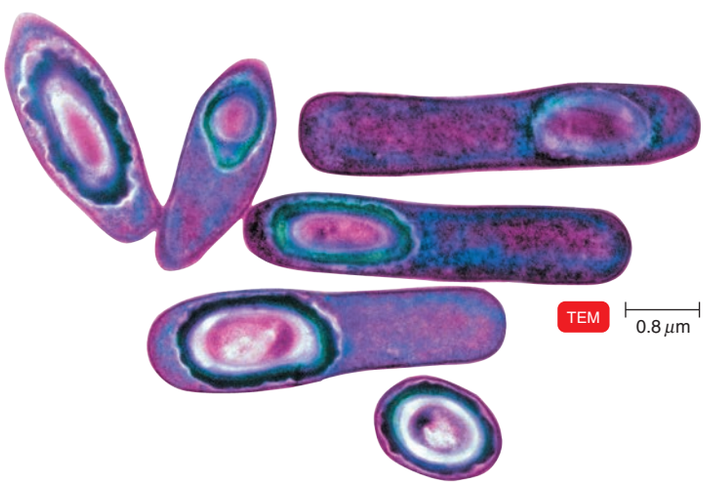
Our bodies are complex sets of ecosystems, with segments that come into contact with the outer world, each having its own microbial population. Our relationship with gut microbiota is usually commensal or mutualistic. However, a change in microbiota can result in dysbiosis, an imbalance that causes adverse effects in the human. For example, *Clostridium difficile,* or C-diff, is usually a minor component of the normal gut microbiota. But when antibiotic therapy kills normal microbiota, C-diff proliferates, producing two toxins that create significant inflammation and gas production in the intestines.

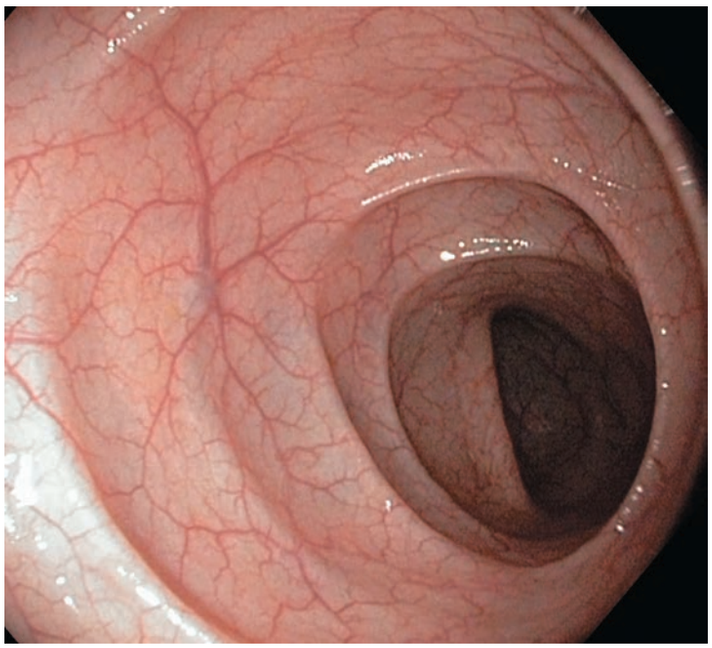
Could Dysbiosis Be the Cause of Inflammatory Bowel Diseases (IBD)?

Dysbiosis is now being closely studied as a possible cause for inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Rationale for this hypothesis hinges on the fact that some metabolic products of normal microbiota, such as butyrates, exert an antiinflammatory effect on the body.

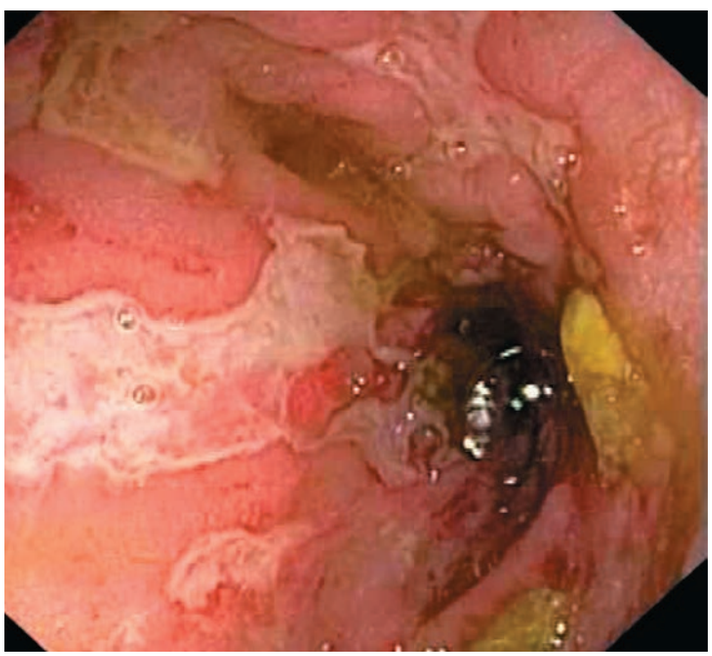
Crohn's disease, whose symptoms include swelling of the GI tract, is often characterized by excessive amounts of the cytokines tumor necrosis factor alpha (TNF-α) and interleukin-12 (IL-12). Researchers hypothesize that this excess could result from a disruption in the balance of normal microbiota that would usually help keep inflammatory cytokines under control.

Another clue being investigated regarding the link between IBD and microbiota is that these diseases are more common in developed countries than less-developed countries. Antibiotic usage tends to be higher in developed countries. Studies have demonstrated that the microbiome may not recover its full diversity after antibiotic treatment, which may lead to loss of organisms that would keep inflammation under control.





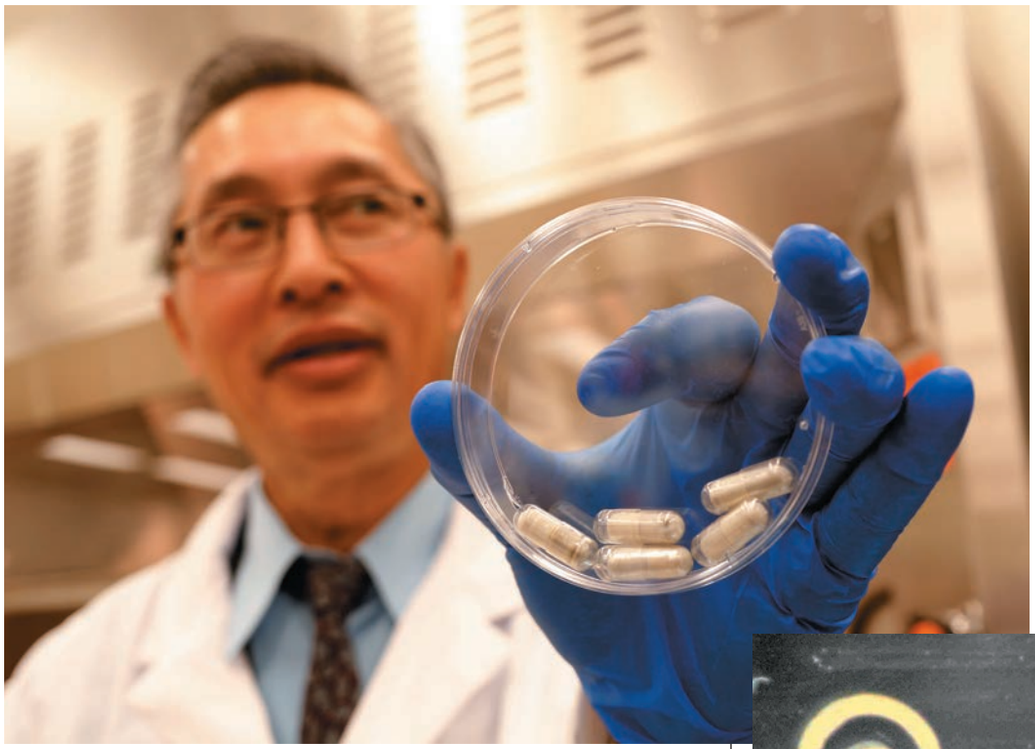
Endoscope view of a healthy colon



Endoscope view of an inflamed and ulcerated colon of a patient with Crohn's disease

Left: *Clostridium difficile,* or C-diff, can proliferate when antibiotics kill normal microbiota, leading to inflammation of the intestines.

Harnessing Microbes to Fight Inflammatory Bowel Diseases



Dr. Thomas Louie at the University of Calgary holds a dish of "poop pills" used for fecal transplantation. Photo credit: Associated Press

Below, eggs of *Trichuris suis*, the pig whipworm used to treat Crohn's disease



Fecal Transplants Shown to Successfully Treat *Clostridium difficile* Infections

Scientists have found success treating C-diff infections and some IBD with fecal microbiota transplants. Fecal transplants involve taking gut microbiota from a healthy individual (usually a family member) and then transplanting it into the patient via an enema, gastroscope, or nasojejunal tube, which is placed through the nose and runs down to the small intestine. Because this technique has been much more effective than antibiotic treatment, the FDA recently relaxed the restrictions it had placed on this procedure.

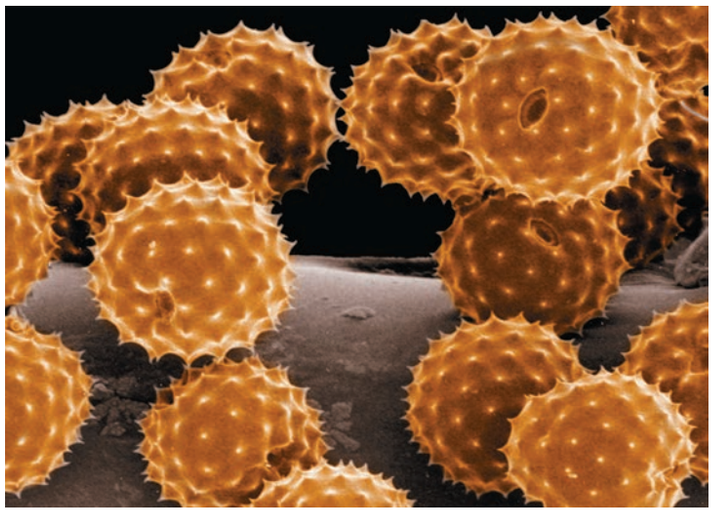
Researchers are working on ways to transplant microbiota in a more palatable fashion. Dr. Thomas Louie, an infectious disease specialist at the University of Calgary, has developed a method to deliver the microbiota in pills surrounded by a triple layer of gel, to prevent breakdown in the stomach. These "poop pills" have been successful in treating his patients with C-diff, and it is hoped that the process can also be used for IBD.

Treating Crohn's Disease with Worms

Hypotheses of how normal microbiota may assist our immune systems have led to some unusual treatments. One clinical study at the University of Iowa, where Crohn's patients were treated with pig whipworm eggs, found a 73% remission rate. Helminths, such as the whipworm, suppress certain T helper cell pathways – the exact pathways that are overactive in Crohn's disease. Since the worms don't take up residence in humans, the treatment must be repeated periodically to maintain the effect.

KEY CONCEPTS

- Normal microbiota are important in maintaining a healthy immune system. **(See Chapter 14, "Relationships Between Normal Microbiota and the Host," pages 391–393.)**
- The Human Microbiome Project is sequencing the genes for 16S ribosomal RNA to help scientists to catalogue normal microbiota that are difficult to culture and identify in the laboratory **(See Chapter 9, "Genome Projects," page 252.)**
- *Trichuris suis* is a roundworm related to *T. trichiura*. **(See Chapter 12, "Nematodes," page 349.)**
- Inflammatory diseases are characterized by increased amounts of cytokines produced by T helper cells, including tumor necrosis factor alpha and interleukins. **(See Chapter 16, "Inflammation," pages 452–455.)**



(a) A micrograph of pollen grains



(b) A micrograph of a house mite on fabric

Figure 19.2 Localized anaphylaxis. Inhaled antigens such as these are a common cause of localized anaphylaxis.

Q Compare localized and systemic anaphylaxis.

antigens introduced via other portals of entry. The release of mediators causes peripheral blood vessels throughout the body to enlarge, resulting in a drop in blood pressure (shock). This reaction can be fatal within a few minutes. There is very little time to act once someone develops systemic anaphylaxis. Treatment usually involves self-administration with a preloaded syringe of epinephrine, a drug that constricts blood vessels and raises the blood pressure. In the United States, 50 to 60 people die each year from anaphylactic shock caused by insect stings.

You may be acquainted with someone who reacts to penicillin in this way. In these individuals, the penicillin, which is a hapten (it cannot induce antibody formation by itself; see Chapter 17), combines with a carrier serum protein. Only then is penicillin immunogenic. Penicillin allergy occurs in about 2% of the population. Skin tests for penicillin sensitivity are available. Patients who have a positive skin test can be desensitized (see page 521) by an orally administered series of increasing doses of penicillin V. The interval between doses is only 15 minutes and is completed within 4 hours. The desensitization is effective only for an uninterrupted penicillin series immediately following the procedure. Allergy to penicillin also includes risk from exposure to some related drugs, such as carbapenem (page 558).

Localized Anaphylaxis

Whereas sensitization to injected antigens is a common cause of systemic anaphylaxis, **localized anaphylaxis** is usually associated with antigens that are ingested (foods) or inhaled (pollen) (**Figure 19.2a**). The symptoms depend primarily on the route by which the antigen enters the body.

In allergies involving the upper respiratory system, such as hay fever, sensitization usually involves mast cells in the mucous membranes of the upper respiratory tract. The airborne antigen might be a common environmental material such as plant pollen, fungal spores, feces of house dust mites (Figure 19.2b), or animal dander.* The typical symptoms are itchy and teary eyes, congested nasal passages, coughing, and sneezing. Antihistamine drugs, which compete for histamine receptor sites, are often used to treat these symptoms.

Asthma is an allergic reaction that mainly affects the lower respiratory system. Symptoms such as wheezing and shortness of breath are caused by the constriction of smooth muscles in the bronchial tubes.

For unknown reasons, asthma is becoming a near epidemic, affecting about 10% of children in Western society, although they often outgrow it. The *hygiene hypothesis,* described previously, may be a factor in the increased incidence of asthma. Mental or emotional stress can be a contributing factor in precipitating an attack. Symptoms of asthma are usually controlled by aerosol inhalants. Xolair (omalizumab) is a newly available drug but is a very expensive treatment for severe allergic asthma. It blocks IgE.

Antigens that enter the body via the gastrointestinal tract can also sensitize an individual. Frequently, so-called food

**Dander* is a general term for microscopic particles from the fur or skin of animals. A cat, for example, carries about 100 mg of dander on its coat and sheds about 0.1 mg a day. This accumulates in upholstery and carpeting. People with allergies to mice, gerbils, and similar small animals are more likely to be allergic to components of urine accumulating in cages.



Figure 19.3 A skin test to identify allergens. Drops of fluid containing test substances are placed on the skin. A light scratch is made with a needle to allow the substances to penetrate the skin. Reddening and swelling at the site identify the substance as a probable cause of an allergic reaction.

Q What is scratched into the skin in a skin test?

allergies may not be related to hypersensitivity at all and are more accurately described as *food intolerances*. For example, many people are unable to digest the lactose in milk because they lack the enzyme that breaks down this disaccharide milk sugar. The lactose enters the intestine, where it osmotically retains fluid, causing diarrhea.

Gastrointestinal upset is a common symptom of food allergies, but it can also result from many other factors. Hives are more characteristic of a true food allergy, and ingestion of the antigen may result in systemic anaphylaxis. Death has even resulted when a person sensitive to fish ate french fries that had been prepared in oil previously used to fry fish. Skin tests are not reliable indicators for diagnosing food-related allergies, and completely controlled tests for hypersensitivity to ingested foods are very difficult to perform. Only eight foods are responsible for 97% of food-related allergies: eggs, peanuts, tree-grown nuts, milk, soy, fish, wheat, and peas. Most children exhibiting allergies to milk, egg, wheat, and soy develop tolerance as they age, but reactions to peanuts, tree nuts, and seafood tend to persist.

An estimated 1.5 million Americans are allergic to peanuts, and as many as 100 deaths occur annually. Therefore, considerable research is under way on the problem, ranging from drugs and vaccines to development of less allergenic peanuts. It is interesting that China has a relatively low incidence of peanut allergy, although peanuts are common in Chinese foods. The reason may be that Chinese cookery involves boiling and lower-temperature frying, whereas dry roasting of peanuts concentrates allergic properties. Some children who have a relatively low level of peanut-specific IgE may outgrow their peanut allergy.

Sulfites, to which many people have an allergy, are a frequent problem. Their use is widespread in foods and beverages; and, although food labels should indicate their presence, they may be difficult to avoid in practice. A food product may have come into contact with a food allergen through processing machinery or cookware previously used for other foods. In one U.S. Food and Drug Administration report, 25% of bakery, ice cream, and candy products tested positive for peanut allergens even though peanuts were not listed on the required product labels. In the United States it is estimated that 200 persons a year die of severe allergic reactions to foods.

Preventing Anaphylactic Reactions

Some individuals experience an allergic reaction after eating an assortment of foods and may not know exactly what food they are sensitive to. In some cases, skin tests might be of use in diagnosis (Figure 19.3). These tests, which are also used for allergies other than those to foods, involve inoculating small amounts of the suspected antigen just beneath the epidermis of the skin. Sensitivity to the antigen is indicated by a rapid inflammatory reaction that produces redness, swelling, and itching at the inoculation site. This small affected area is called a *wheal*.

Once the responsible antigen has been identified, the person can either try to avoid contact with it or undergo **desensitization.** This procedure usually consists of a series of gradually increasing dosages of the antigen carefully injected beneath the skin. The objective is to cause the production of IgG rather than IgE antibodies in the hope that the circulating IgG antibodies will act as *blocking antibodies* to intercept and neutralize the antigens before they can react with cell-bound IgE. Desensitization is not a routinely successful procedure, but it is effective in 65–75% of individuals whose allergies are induced by inhaled antigens and in a reported 97% of people allergic to insect venom.

Clinical Case

The emergency department physician quickly rules out erythema infectiosum (fifth disease) because the rash did not begin on his face. (Fifth disease is a viral illness; one of the first symptoms is a facial rash.) Malik has no other symptoms (e.g., difficulty breathing, low blood pressure) that would indicate an anaphylactic reaction. When speaking with the parents, the physician finds out that Malik recently underwent surgery to repair a heart defect and was given a routine blood transfusion. During the surgery it was discovered that Malik doesn't have a thymus gland.

What is the role of the thymus gland? (Hint: See Chapter 17.)

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TABLE 19.2 The ABO Blood Group System

Blood Group	Erythrocyte or Red Blood Cell Antigens	Illustration	Plasma Antibodies	Cells That Can Be Received	Frequency (% U.S. Population)		
					White	Black	Asian
A	A		Anti-B	A, O	41	27	28
B	B		Anti-A	B, O	9	20	27
AB	A and B		Neither anti-A nor anti-B antibodies	A, B, AB, O	3	4	5
O	Neither A nor B		Anti-A and Anti-B	O	47	49	40

CHECK YOUR UNDERSTANDING

- In what tissues do we find the mast cells that are major contributors to allergic reactions such as hay fever? **19-2**
- Which is the more dangerous to life: systemic or localized anaphylaxis? **19-3**
- How can we tell whether a person is sensitive to a particular allergen, such as a tree pollen? **19-4**
- Which antibody types need to be blocked to desensitize a person subject to allergies? **19-5**

Type II (Cytotoxic) Reactions

Type II (cytotoxic) reactions generally involve the activation of complement by the combination of IgG or IgM antibodies with an antigenic cell. This activation stimulates complement to lyse the affected cell, which might be either a foreign cell or a host cell that carries a foreign antigenic determinant (such as a drug) on its surface. Additional cellular damage may be caused within 5 to 8 hours by the action of macrophages and other cells that attack antibody-coated cells.

The most familiar cytotoxic hypersensitivity reactions are *transfusion reactions,* in which red blood cells are destroyed as a result of reacting with circulating antibodies. These involve blood group systems that include the ABO and Rh antigens.

The ABO Blood Group System

In 1901, Karl Landsteiner discovered that human blood could be grouped into four principal types, which were designated A, B, AB, and O. This method of classification is called the **ABO blood group system.** Since then, other blood group systems, such as the Lewis system and the MN system, have been discovered, but our discussion will be limited to two of the best known, the ABO and the Rh systems. The main features of the ABO blood group system are summarized in **Table 19.2**.

A person's ABO blood type depends on the presence or absence of carbohydrate antigens located on the cell membranes of red blood cells (RBCs). Cells of blood type O lack both A and B antigens. Table 19.2 shows that the plasma of individuals with a given blood type, such as A, have antibodies against the alternative blood type, anti-B antibody. These antibodies are presumed to arise in response to microorganisms and ingested foodstuffs that have antigenic determinants very similar to blood group antigens. Individuals with type AB cells have plasma with no antibodies to either A or B antigens. Type O individuals have antibodies against both A and B antigens. (Blood banking is discussed in the box in Chapter 25 on page 730.)

When a transfusion is incompatible, as when type B blood is transfused into a person with type A blood, the antigens on the type B blood cells will react with anti-B antibodies in the recipient's serum. This antigen–antibody reaction activates complement, which in turn causes lysis of the donor's RBCs as they enter the recipient's system.

A relationship between blood types and certain diseases has been observed, which may be related to the skewing of blood types in the population of certain geographical areas. For example, individuals with type O blood are more susceptible to the incidence and severity of cholera and other diarrheas, whereas individuals with type B are much less affected. This tendency seems to be reflected in the blood types found in the Indian subcontinent, where type B is common and type O less so. Iceland has a relatively low percentage of blood types A and AB, possibly caused by the greater susceptibility of these blood types to a succession of smallpox epidemics within this geographically

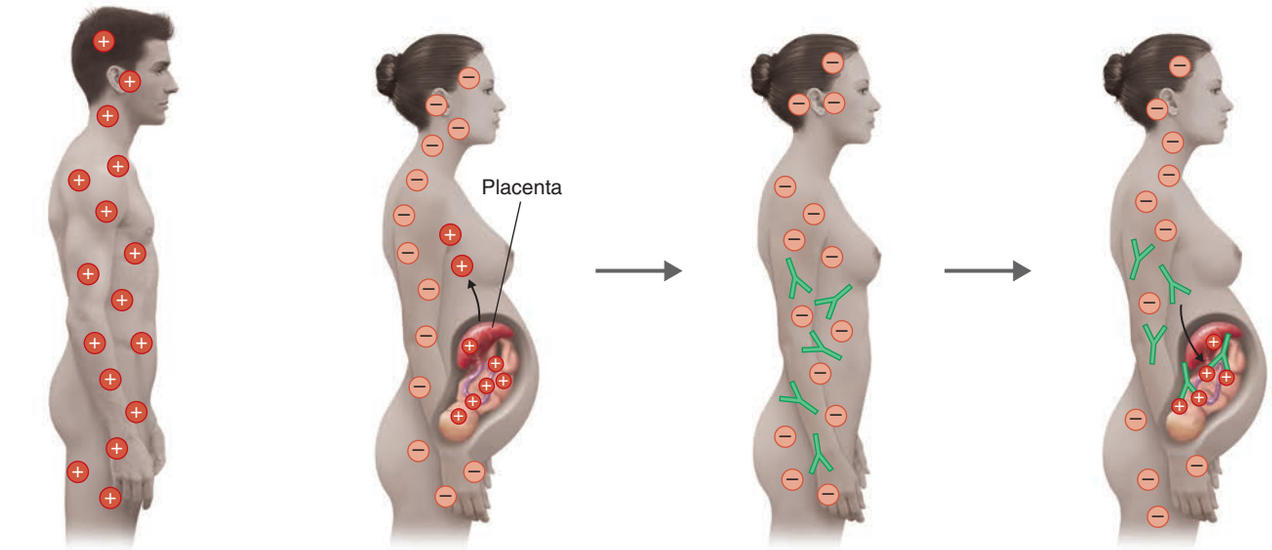


Figure 19.4 Hemolytic disease of the newborn.

Q What type of antibodies cross the placenta?

restricted population. More than half of the population of tropical Africa is of type O, which tends to be less severely affected by malaria.

The Rh Blood Group System

In the 1930s, researchers discovered the presence of a different surface antigen on human red blood cells. Soon after they injected rabbits with RBCs from rhesus monkeys, the rabbit serum contained antibodies that were directed against the monkey blood cells but that would also agglutinate some human RBCs. This indicated that a common antigen was present on both human and monkey red blood cells. The antigen was named the **Rh factor** (*Rh* for rhesus monkey). The roughly 85% of the population whose cells possess this antigen are called Rh^+; those lacking this RBC antigen (about 15%) are Rh^-. Antibodies that react with the Rh antigen do not occur naturally in the serum of Rh^- individuals, but exposure to this antigen can sensitize their immune systems to produce anti-Rh antibodies.

Blood Transfusions and Rh Incompatibility If blood from an Rh^+ donor is given to an Rh^- recipient, the donor's RBCs stimulate the production of anti-Rh antibodies in the recipient. If the recipient then receives Rh^+ RBCs in a subsequent transfusion, a rapid, serious hemolytic reaction will develop.

Hemolytic Disease of the Newborn Blood transfusions are not the only way in which an Rh^- person can become sensitized to Rh^+ blood. When an Rh^- woman and an Rh^+ man produce a child, there is a 50% chance that the child will be Rh^+ (Figure 19.4). If the child is Rh^+, the Rh^- mother can become sensitized to this antigen during birth when the placental membranes tear and the fetal Rh^+ RBCs enter the maternal circulation, causing the mother's body to produce anti-Rh antibodies of the IgG type. If the fetus in a subsequent pregnancy is Rh^+, the mother's anti-Rh antibodies will cross the placenta and destroy the fetal RBCs. The fetal body responds to this immune attack by producing large numbers of immature RBCs called erythroblasts. Thus, the term *erythroblastosis fetalis* was once used to describe what is now called **hemolytic disease of the newborn (HDNB).** Before the birth of a fetus with this condition, the maternal circulation removes most of the toxic by-products of fetal RBC disintegration. After birth, however, the fetal blood is no longer purified by the mother, and the newborn develops jaundice and severe anemia.

HDNB is usually prevented today by passive immunization of the Rh^- mother at the time of delivery of any Rh^+ infant with anti-Rh antibodies, which are available commercially (RhoGAM). These anti-Rh antibodies combine with any fetal Rh^+ RBCs that have entered the mother's circulation, so it is much less likely that she will become sensitized to the Rh antigen. If the disease is not prevented, the newborn's Rh^+ blood, contaminated with maternal antibodies, may have to be replaced by transfusion of uncontaminated blood.

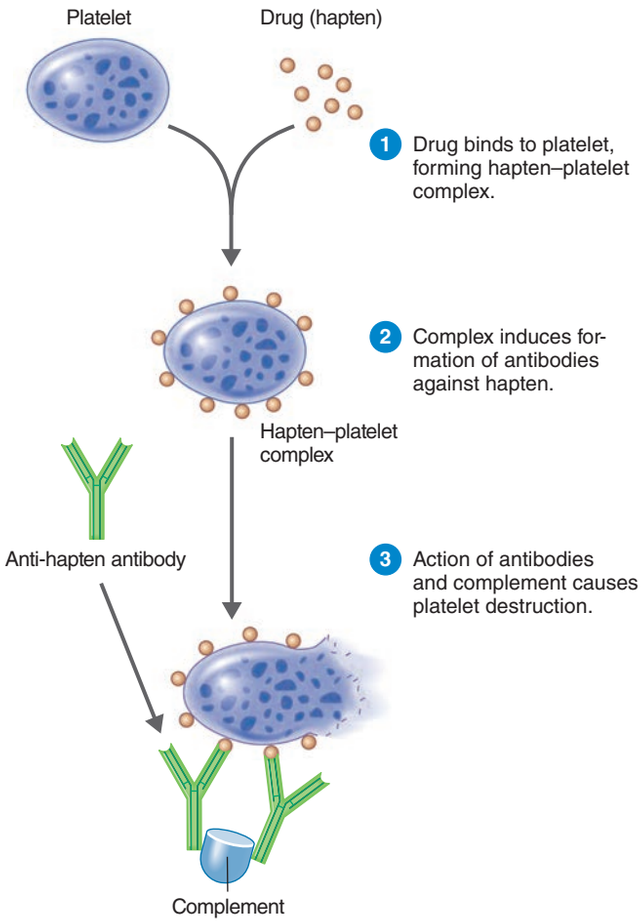


Figure 19.5 Drug-induced thrombocytopenic purpura. Molecules of a drug such as quinine accumulate on the surface of a platelet and stimulate an immune response that destroys the platelet.

Q What actually destroys the platelets in thrombocytopenic purpura?

Drug-Induced Cytotoxic Reactions

Blood platelets (thrombocytes) are minute cell-like bodies that are destroyed by drug-induced cytotoxic reactions in the disease called **thrombocytopenic purpura.** The drug molecules are usually haptens because they are too small to be antigenic by themselves. In the situation illustrated in Figure 19.5, a platelet has become coated with molecules of a drug (quinine is a familiar example), and the combination is antigenic. Both antibody and complement are needed for lysis of the platelet. Because platelets are necessary for blood clotting, their loss results in hemorrhages that appear on the skin as purple spots (purpura).

Drugs may bind similarly to white or red blood cells, causing local hemorrhaging and yielding symptoms described as "blueberry muffin" skin mottling. Immune-caused destruction of granulocytic white cells is called **agranulocytosis,** and it affects the body's phagocytic defenses. When RBCs are destroyed in the same manner, the condition is termed **hemolytic anemia.**

CHECK YOUR UNDERSTANDING

- What, besides an allergen and an antibody, is required to precipitate a cytotoxic reaction? 19-6
- What are the antigens located on the cell membranes of type O blood? 19-7
- If a fetus that is Rh^+ can be damaged by anti-Rh antibodies of the mother, why does such damage never happen during the first such pregnancy? 19-8

Type III (Immune Complex) Reactions

Type III reactions involve antibodies against soluble antigens circulating in the serum. (In contrast, type II immune reactions are directed against antigens located on cell or tissue surfaces.) The antigen–antibody complexes are deposited in organs and cause inflammatory damage.

Immune complexes form only when certain ratios of antigen and antibody occur. The antibodies involved are usually IgG. A significant excess of antibody leads to the formation of complement-fixing complexes that are rapidly removed from the body by phagocytosis. When there is a significant excess of antigen, soluble complexes form that do not fix complement and do not cause inflammation. However, when a certain antigen–antibody ratio exists, usually with a slight excess of antigen, the soluble complexes that form are small and escape phagocytosis.

Figure 19.6 illustrates the consequences. These complexes circulate in the blood, pass between endothelial cells of the blood vessels, and become trapped in the basement membrane beneath the cells. In this location, they may activate complement

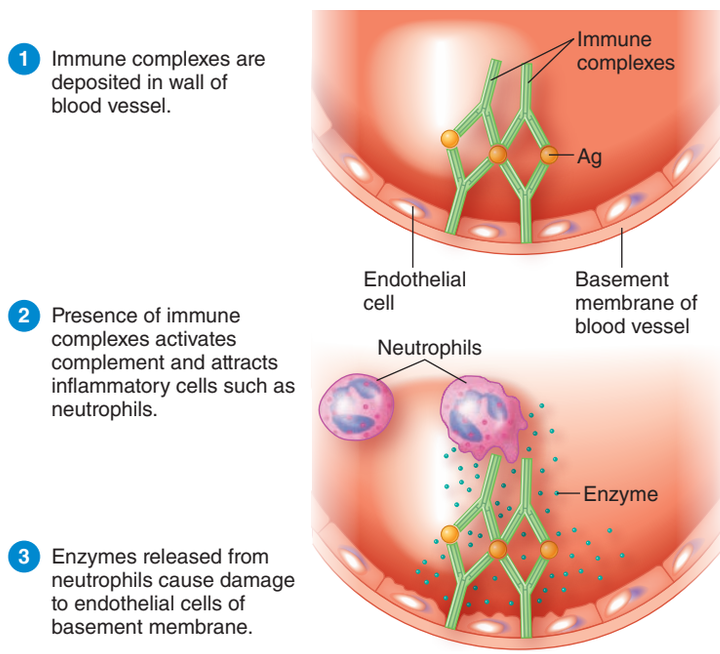


Figure 19.6 Immune complex–mediated hypersensitivity.

Q Name one immune complex disease.

and cause a transient inflammatory reaction: attracting neutrophils that release enzymes. Repeated introduction of the same antigen can lead to more serious inflammatory reactions, causing damage to the basement membrane's endothelial cells within 2 to 8 hours.

Glomerulonephritis is an immune complex condition, usually resulting from an infection, that causes inflammatory damage to the kidney glomeruli, which are sites of blood filtration.

CHECK YOUR UNDERSTANDING

Are the antigens causing immune complex reactions soluble or insoluble? **19-9**

Type IV (Delayed Cell-Mediated) Reactions

Up to this point we have discussed humoral immune responses involving IgE, IgG, or IgM. Type IV reactions involve cell-mediated immune responses and are caused mainly by T cells. **Delayed cell-mediated reactions** (or **delayed hypersensitivity**) are not apparent for a day or more. A major factor in the delay is the time required for the participating T cells and macrophages to migrate to and accumulate near the foreign antigens. Transplant rejection is most commonly mediated by cytotoxic T lymphocytes (CTLs), but other mechanisms are by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-mediated lysis. Another example is described in the Clinical Focus box on page 527.

Causes of Delayed Cell-Mediated Reactions

Sensitization for delayed hypersensitivity reactions occurs when certain foreign antigens, particularly those that bind to tissue cells, are phagocytized by macrophages and then presented to receptors on the T-cell surface. Contact between the antigenic determinant sites and the appropriate T cell causes the T cell to proliferate into mature differentiated T cells and memory cells.

When a person sensitized in this way is reexposed to the same antigen, a delayed hypersensitivity reaction might result. Memory cells from the initial exposure activate T cells, which release destructive cytokines in their interaction with the target antigen. In addition, some cytokines contribute to the inflammatory reaction to the foreign antigen by attracting macrophages to the site and activating them.

Delayed Cell-Mediated Hypersensitivity Reactions of the Skin

One delayed hypersensitivity reaction that involves the skin is the familiar skin test for tuberculosis. Because *Mycobacterium tuberculosis* is often located within macrophages, this organism can stimulate a delayed cell-mediated immune response. As a screening test, protein components of the bacteria are injected into the skin. If the recipient has (or has had) a previous infection by tuberculosis bacteria, an inflammatory reaction to the injection of these antigens will appear in 1 to 2 days (see Figure 24.9, page 687); this interval is typical of delayed hypersensitivity reactions.

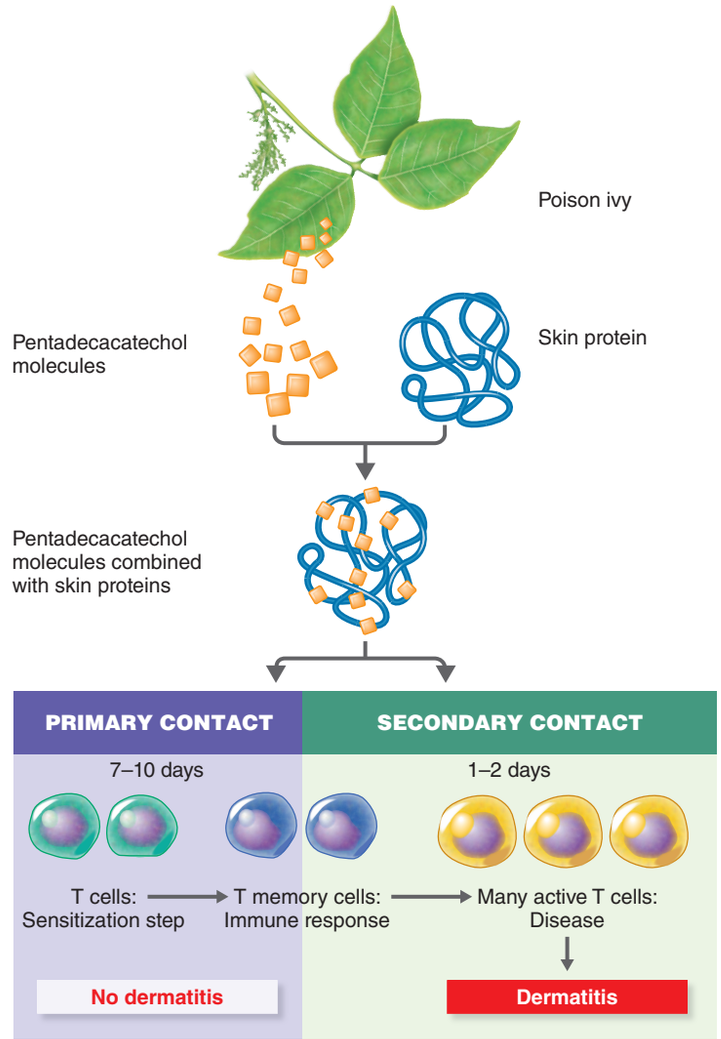


Figure 19.7 The development of an allergy (allergic contact dermatitis) to catechols from the poison ivy plant. Pentadecacatechol is a mixture of catechols, which are oils secreted by the plant that dissolve easily in skin oils and penetrate the skin. In the skin, the catechols function as haptens—that is, they combine with skin proteins to become antigenic and provoke an immune response. The first contact with poison ivy sensitizes the susceptible person, and subsequent exposure results in contact dermatitis.

How does a hapten cause an allergic reaction?

Allergic contact dermatitis, another common manifestation of delayed cell-mediated hypersensitivity, is usually caused by haptens that combine with proteins (particularly the amino acid lysine) in the skin of some people to produce an immune response. Reactions to poison ivy (**Figure 19.7**), cosmetics, and the metals in jewelry (especially nickel) are familiar examples of these allergies.

The increasing exposure to latex in condoms, in certain catheters, and in gloves used by health care workers has led to a greater awareness of hypersensitivity to latex. Death from anaphylactic shock can also occur. Many hospitals now even restrict entry of latex balloons.



Figure 19.8 Allergic contact dermatitis. This person's hand exhibits a severe case of delayed contact dermatitis from wearing latex surgical gloves.

Q What is allergic contact dermatitis?

Among physicians and nurses, 5–12% report this type of hypersensitivity to latex surgical gloves (Figure 19.8). Synthetic polymers such as vinyl and, especially, nitrile are alternatives to latex, but even nitrile gloves occasionally cause allergic reactions. Most gloves that are made of natural latex, as well as those made of nitrile and neoprene, contain chemical additives called accelerators. Accelerators promote cross-linkage, which adds strength and resiliency, but they have been implicated in allergic reactions. One type of nitrile glove that does not contain accelerators has been developed and has received U.S. Food and Drug Administration (FDA) registration as a Class II medical device that can be labeled as nonallergenic. Another alternative glove has been recently approved. It is a product of the guayule (wī-Ū-Iē) shrub that is native to arid areas of the U.S. Southwest. It does not contain latex allergens.

Many persons who develop an allergy to latex for some reason also have evidence of allergies to certain fruits, most commonly avocado, chestnut, banana, and kiwi. Latex paint, however, does not pose a threat of hypersensitivity reactions. Despite its name, latex paint contains no natural latex, but only synthetic nonallergenic chemical polymers.

The identity of the environmental factor causing the dermatitis can usually be determined by a *patch test.* Samples of suspected materials are taped to the skin; after 48 hours, the area is examined for inflammation.

CHECK YOUR UNDERSTANDING

What is the primary reason for the delay in a delayed cell-mediated reaction? **19-10**

Autoimmune Diseases

LEARNING OBJECTIVES

19-11 Describe a mechanism for self-tolerance.

19-12 Give an example of immune complex, cytotoxic, and cell-mediated autoimmune diseases.

When the action of the immune system is in response to self-antigens and causes damage to one's own organs, the result is an **autoimmune disease.** More than 40 autoimmune diseases have been identified. Although relatively rare, they affect about 5% of the population in the developed world.

About 75% of the cases of autoimmune disease selectively affect women. Reasons for this are still being explored, but autoantibody-producing B cells are more abundant in female mice than male ones. Moreover, the number of cells increases as female mice age but stays at constant levels in males. Researchers also found these cells activate via a Toll-like receptor encoded on the X chromosome. Since woman have two X chromosomes (though one is usually silenced), this may lead women to express higher levels of some X-chromosome genes compared to men, who have a single X chromosome. Treatments for autoimmune diseases are improving as knowledge of the mechanisms controlling immune reactions improves.

Autoimmune diseases occur when there is a loss of **self-tolerance,** the immune system's ability to discriminate self from nonself. In the generally accepted model by which T cells become capable of distinguishing self from nonself, the cells acquire this ability during their passage through the thymus. Any T cells that will target host cells are eliminated by *thymic selection* during this period (as we saw in Chapter 17, page 479). This step makes it unlikely that the T cell will attack its own tissue cells.

In autoimmune diseases, the loss of self-tolerance leads to the production of antibodies or a response by sensitized T cells against a person's own tissue antigens. Autoimmune reactions, and the diseases they cause, can be cytotoxic, immune complex, or cell-mediated in nature.

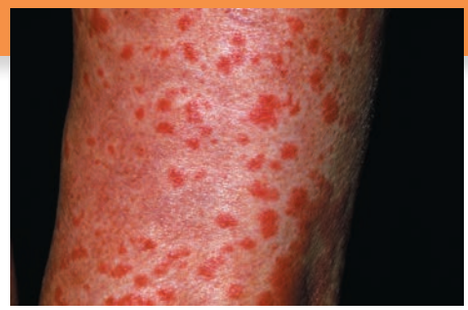
Cytotoxic Autoimmune Reactions

Graves' disease is a condition in which the thyroid gland is stimulated to produce increased amounts of thyroid hormones. Normally, the pituitary gland in the brain releases a hormone called thyroid-stimulating hormone (TSH). However, in Graves' disease there is a malfunction of the immune system, and abnormal antibodies are released that mimic TSH. These abnormal antibodies cause the thyroid to produce excessive amounts of hormones, causing pounding of the heart, trembling, and sweating. The most striking external signs of the disease are goiter (a disfiguring swelling of the thyroid gland in the neck) and markedly bulging, staring eyes.

Myasthenia gravis is a disease in which muscles become progressively weaker. It is caused by antibodies that coat the

CLINICAL FOCUS

A Delayed Rash



As you read through this box, you will encounter a series of questions that health care professionals ask as they determine the cause of a patient's symptoms. Try to answer each question before going on to the next one.

1. A 65-year-old woman with hip and shoulder replacements made a routine dental appointment. She asked for her usual prescription of cephalothin. The nurse practitioner prescribed penicillin, saying it is less expensive. Because of her hip and shoulder implants, antibiotics were prescribed for 2 days after any dental work.
   Why are patients with medical implants more susceptible to infection from dental work?
2. Oral bacteria introduced to the bloodstream during dental work can colonize on medical implants. The resulting biofilm may be a source of serious systemic infections. The dental cleaning went well. Seven days later, the woman developed a maculopapular rash over her legs and torso (see the photo).
   What are the most likely causes of a rash, in the absence of fever or other signs of infection?
3. A rash is likely due to an allergic reaction.
   What questions would you ask the patient?
4. The patient had not tried any new foods, cleaning agents, or clothing. She said the only thing different during the past 10 days was her taking the penicillin. The nurse practitioner said penicillin couldn't be the cause because responses to penicillin occur within minutes to hours after exposure.
   Was the nurse practitioner correct?
5. Immediate reactions that occur within minutes to hours suggest an antibody-mediated allergy. Delayed reactions, such as in this patient, that occur after days to weeks suggest a type IV cell-mediated reaction.
   What cells are responsible for a type IV hypersensitivity? What antibodies are involved in a type I hypersensitivity?
6. Sensitized T cells are involved in delayed hypersensitivity reactions, including antibiotic-induced rashes. Drug-specific IgE antibodies are responsible for type I immediate hypersensitivity reactions.
   What should the nurse practitioner have asked?
7. The nurse practitioner should have asked whether the patient had any drug allergies. However, in this case, the patient had no prior drug-induced allergy.
   Was this the patient's first exposure to penicillin?
8. Allergic reactions do not occur on the first exposure to an antigen. The prior exposure could have occurred once during the patient's life. Many immunologists feel that the overuse of penicillin 40 years ago for bacterial infections resulted in an increased frequency of allergic reactions. Most patients who have a history of penicillin allergy, however, will tolerate cephalosporins.

acetylcholine receptors at the junctions at which nerve impulses reach the muscles. Eventually, the muscles controlling the diaphragm and the rib cage may fail to receive the necessary nerve signals, and respiratory arrest and death result.

Both diseases involve antibody reactions to cell-surface antigens, although there is no cytotoxic destruction of the cells.

Immune Complex Autoimmune Reactions

Systemic lupus erythematosus is a systemic autoimmune disease, involving immune complex reactions, that mainly affects women. The etiology of the disease is not completely understood, but afflicted individuals produce antibodies directed at components of their own cells, including DNA, which is probably released during the normal breakdown of tissues, especially the skin. The most damaging effects of the disease result from deposits of immune complexes in the kidney glomeruli.

Crippling **rheumatoid arthritis** is a disease in which immune complexes of IgM, IgG, and complement are deposited in the joints. In fact, immune complexes called *rheumatoid factors* may be formed by IgM binding to the Fc region of normal IgG. These factors are found in 70% of individuals suffering from rheumatoid arthritis. The chronic inflammation caused by this deposition eventually leads to severe damage to the cartilage and bone of the joint.

Cell-Mediated Autoimmune Reactions

Multiple sclerosis is one of the more common autoimmune diseases, affecting mostly younger adults. Most individuals with multiple sclerosis are whites living in northern latitudes; women are twice as likely to have the disease. It is a neurological disease in which T cells and macrophages attack the myelin sheath of nerves. Symptoms range from only fatigue and weakness to, in some cases, eventual severe paralysis. The disease progresses slowly, over many years. New attacks that worsen the condition are often separated by long periods of remission. There is considerable evidence of genetic susceptibility, probably not from a single gene, but from several genes that interact. The etiology of multiple sclerosis is unknown, but epidemiological evidence indicates that it probably involves some infective agent or agents acquired during early adolescence. The Epstein-Barr virus (page 381) is frequently mentioned as a prime suspect. No cure exists, but treatments with interferons and several drugs that interfere with immune processes can significantly slow progression of symptoms.

TABLE 19.3 Diseases Related to Specific Human Leukocyte Antigens (HLAs)

Disease	Increased Risk of Occurrence with Specific HLA*	Description
INFLAMMATORY DISEASES		
Multiple sclerosis	5 times	Progressive inflammatory disease affecting nervous system
Rheumatic fever	4–5 times	Cross-reaction with antibodies against streptococcal antigen
ENDOCRINE DISEASES		
Addison's disease	4–10 times	Deficiency in production of hormones by adrenal gland
Graves' disease	10–12 times	Disorder in which antibodies attached to certain receptors in the thyroid gland cause it to enlarge and produce excessive hormones
MALIGNANT DISEASE		
Hodgkin's disease	1.4–1.8 times	Cancer of lymph nodes

*Compared to the general population.

Insulin-dependent diabetes mellitus is a familiar condition caused by immunological destruction of insulin-secreting cells of the pancreas. T cells are clearly implicated in this disease; animals that are genetically likely to develop diabetes fail to do so when their thymus is removed in infancy.

The fairly common skin condition **psoriasis** is an autoimmune disorder characterized by itchy, red patches of thickened skin. As many as 25% of patients develop **psoriatic arthritis.** Several topical and systemic therapies such as corticosteroids and methotrexate are available to help control psoriasis of the skin. Psoriasis is considered to be a T_H1 disease and can be treated effectively with immunosuppressants that target T cells and especially the cytokine, TNF-α (see page 453), an important factor in inflammation. For psoriatic arthritis, as well as rheumatoid arthritis, the most effective treatments are injections of monoclonal antibodies that inhibit TNF-α. See the Applications of Microbiology box in Chapter 17 on page 471 for another new treatment.

CHECK YOUR UNDERSTANDING

- What is the importance of clonal deletion in the thymus? **19-11**
- What organ is affected in Graves' disease? **19-12**

Reactions Related to the Human Leukocyte Antigen (HLA) Complex

LEARNING OBJECTIVES

19-13 Define *HLA complex,* and explain its importance in disease susceptibility and tissue transplants.

19-14 Explain how a transplant is rejected.

19-15 Define *privileged site*.

19-16 Discuss the role of stem cells in transplantation.

19-17 Define *autograft, isograft, allograft,* and *xenotransplant*.

19-18 Explain how graft-versus-host disease occurs.

19-19 Explain how rejection of a transplant is prevented.

The inherited genetic characteristics of individuals are expressed not only in the color of their eyes and the curl of their hair but also in the composition of the self molecules on their cell surfaces. Some of these are called **histocompatibility antigens.** The genes controlling the production of the most important of these self molecules are known as the **major histocompatibility complex (MHC).** In humans, these genes are called the **human leukocyte antigen (HLA) complex.** We encountered these self molecules in Chapter 17 (page 475), where we saw that most antigens can stimulate an immune reaction only if they are associated with an MHC molecule.

A process called *HLA typing* is used to identify and compare HLAs. Certain HLAs are related to an increased susceptibility to specific diseases; one medical application of HLA typing is to identify such susceptibility. A few of these relationships are summarized in **Table 19.3**.

Another important medical application of HLA typing is in transplant surgery, in which the donor and the recipient must be matched by *tissue typing.* The serological technique shown in **Figure 19.9** is the one most often used. In serological tissue typing, the laboratory uses standardized antisera or monoclonal antibodies that are specific for particular HLAs.

A newer, more accurate technique for analyzing HLA is the use of *polymerase chain reaction* (PCR) to amplify the cell's DNA (see Figure 9.4, page 244). If this is done for both donor and recipient, a match between donor DNA and recipient DNA can then be made. Having such a DNA match and matching ABO blood type between the donor and the recipient should result in a much higher success rate in transplant surgery.

Other factors may be involved in the success of a transplant, however. According to one hypothesis, the body's reaction to

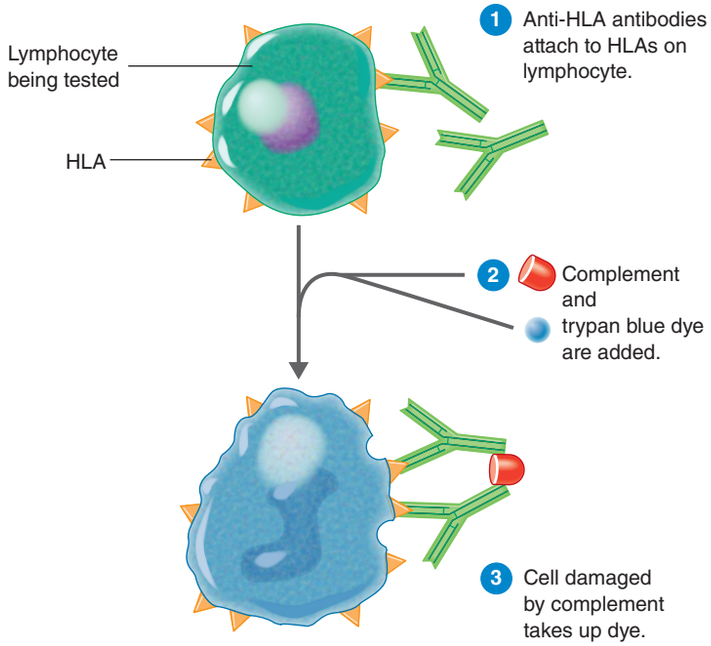


Figure 19.9 Tissue typing, a serological method. Lymphocytes from the person being tested are incubated with laboratory test stocks of anti-HLA antibodies specific for a particular HLA. If the antibodies react with the antigens on a lymphocyte, then complement damages the lymphocyte, and dye can enter the cell. Such a positive test result indicates that the person has the particular HLA being tested for.

Q Why is tissue typing done?

transplanted foreign tissue may be a response to surgery-damaged cells. In other words, tissue rejection may result from a learned reaction to the danger signal posed by damaged cells, rather than a learned reaction to nonself.

CHECK YOUR UNDERSTANDING

What is the relationship between the major histocompatibility complex in humans and the human leukocyte antigen complex? **19-13**

Reactions to Transplantation

In sixteenth-century Italy, crimes were often punished by cutting off the offender's nose. A surgeon of the time, in his attempts to repair this mutilation, observed that if skin was taken from the patient, it healed properly, but if it was taken from another person, it did not. He called this a manifestation of "the force and power of individuality."

We now know the principles behind this phenomenon. Transplants recognized as nonself are rejected—attacked by T cells that directly lyse the grafted cells, by macrophages activated by T cells, and, in certain cases, by antibodies, which activate the complement system and injure blood vessels supplying the transplanted tissue. However, transplants that are not rejected can add many healthy years to a person's life.

Since the first kidney transplant was performed in 1954, this particular type of transplant has become a nearly routine medical procedure. Other types of transplants that are now feasible include bone marrow, lungs, heart, liver, and cornea. Tissues and organs for transplant are usually taken from recently deceased individuals, although one of a pair of organs, such as a kidney, occasionally comes from a living donor. A donor can also donate as much as half of a healthy liver.

Privileged Sites and Privileged Tissue

Some transplants or grafts do not stimulate an immune response. A transplanted cornea, for example, is rarely rejected, mainly because antibodies usually do not circulate into that portion of the eye, which is therefore considered an immunologically **privileged site.** (However, rejections do occur, especially when the cornea has developed many blood vessels from corneal infections or damage.) The brain is also an immunologically privileged site, probably because it does not have lymphatic vessels and because the walls of the blood vessels in the brain differ from blood vessel walls elsewhere in the body (the blood–brain barrier is discussed in Chapter 22). Someday it may even be possible to graft foreign nerves to replace damaged nerves in the brain and spinal cord.

It is possible to transplant **privileged tissue,** which does not stimulate an immune rejection. An example is replacing a person's damaged heart valve with a valve from a pig's heart. However, privileged sites and tissues are more the exception than the rule.

Transplanted privileged tissue from a pig requires that the pig tissue be modified by decellularization, meaning that the pig tissue's antigenic cellular elements are removed either physically or chemically.

How animals tolerate pregnancy without rejecting the fetus is only partially understood. During pregnancy, the tissues of two genetically different individuals are in direct contact. An important factor seems to be that the MHC classes I and II in the cells that form the outer layer of the placenta—and come into contact with maternal tissue—are not of the specific types that stimulate a cellular immune response. The fetus is also protected by certain proteins it synthesizes, which have immunosuppressive properties. But there is no single, simple explanation.

Stem Cells

A development that promises to transform transplantation medicine is the use of **stem cells** (see Figure 17.1, page 470), master cells that are capable of generating 200-plus cell types, such as skin, bone, or blood, that make up the body. Speaking generally, there are **embryonic stem cells (ESCs),** which can be harvested from blastocysts (**Figure 19.10**), and **adult stem cells,** which are found in various tissues. In the medical community, use of ESCs in therapy is a topic that attracts great interest. For example, theoretically these cells could be used to regenerate

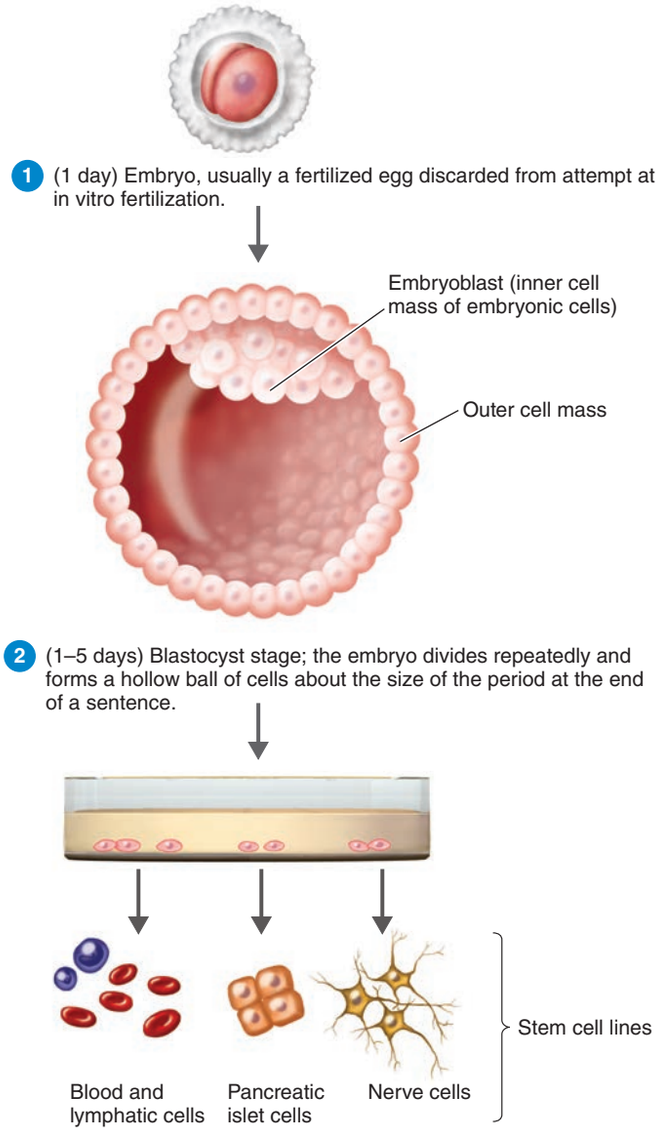


Figure 19.10 Derivation of embryonic stem cells.

Q What does *pluripotent* mean?

damaged heart tissue or the failing insulin-producing cells in the pancreas that lead to diabetes. Damaged cartilage in the joints of rheumatoid arthritis patients might be replaced. There is even the prospect of growing complete new organs.

The nomenclature employed reflects the potential of various stem cells. If a cell can generate all types of cells, it is termed *pluripotent*. These cells naturally occur in mammals only very early in embryo development—hence their other name, *embryonic stem cells*. It is now possible to create **induced pluripotent stem cells (iPSCs)** in the laboratory. These are made by introducing regulatory genes by transduction or by adding the regulatory proteins to culture media. When these cells are isolated and grown in culture, they give rise to embryonic stem cells.

Later in embryonic development, stem cells specialize and are able to give rise only to specific families of cell types, such as blood, skin, or muscle. These cells are called *multipotent*. After birth, these multipotent stem cells are called *adult stem cells*. They replenish cells, as needed, for various body organs. For instance, skin stem cells continue to grow skin and hair.

Grafts

When one's own tissue is grafted to another part of the body, as is done in burn treatment or in plastic surgery, the graft is not rejected. Recent technology has made it possible to use a few cells of a burn patient's uninjured skin to culture extensive sheets of new skin. This new skin is an example of an **autograft**. Identical twins have the same genetic makeup; therefore, skin or organs such as kidneys may be transplanted between them without provoking an immune response. Such a transplant is called an **isograft.**

Most transplants, however, are made between people who are not identical twins, and these transplants do trigger an immune response. Attempts are made to match the HLAs of the donor and recipient as closely as possible to reduce the chances of rejection. Because HLAs of close relatives are most likely to match, blood relatives, especially siblings, are the preferred donors. Grafts between people who are not identical twins are called **allografts.**

Because of the shortage of available organs, medical researchers hope to increase the success of **xenotransplantation products** (formerly called **xenografts**), which are tissues or organs that have been transplanted from animals. However, the body tends to mount an especially severe immune assault on such transplants. Unsatisfactory attempts have been made to use organs from baboons and other nonhuman primates. Research interest is high in genetically modifying pigs—an animal that is in plentiful supply, is of the right size, and generates relatively little public sympathy—to make acceptable donors of organs. The primary concern about xenotransplantation products is the possibility of transferring harmful animal viruses.

Preliminary research is under way that may eventually allow some bones and organs to be grown from the host's own tissue cells.

To be successful, xenotransplantation products must overcome **hyperacute rejection,** caused by the development in early infancy of antibodies against all distantly related animals such as pigs. With the aid of complement, these antibodies attack the transplanted animal tissue and destroy it within an hour. Hyperacute rejection occurs in human-to-human transplants only when antibodies have been preformed because of previous transfusions, transplantations, or pregnancies. Liver

transplantation among humans is unusual in one respect; this organ usually resists hyperacute rejection, and HLA typing is not as important as in other types of tissue.

Bone Marrow Transplants

Transplants of bone marrow, now often known as *hemapoietic stem cell transplants,* are frequently in the news. The recipients are usually individuals who lack the capacity to produce B cells and T cells vital for immunity or who are suffering from leukemia. Bone marrow stem cells give rise to red blood cells and immune system lymphocytes (see Chapter 17). The goal of bone marrow transplants is to enable the recipient to produce healthy red blood, or immune system, cells. However, such transplants can result in **graft-versus-host (GVH) disease.** The transplanted bone marrow contains immunocompetent cells that mount primarily a cell-mediated immune response against the tissue into which they have been transplanted. Because the recipients lack effective immunity, GVH disease is a serious complication and can even be fatal.

An extremely promising technique for avoiding this problem is the use of *umbilical cord blood* instead of bone marrow. This blood is harvested from the placenta and umbilical cords of newborns, material that would otherwise be discarded. It is very rich in the stem cells found in bone marrow. Not only do these cells proliferate into the variety of cells required by the recipient, but also, because stem cells from this source are younger and less mature, the "matching" requirements are also less stringent than with bone marrow. As a result, GVH disease is less likely to occur.

CHECK YOUR UNDERSTANDING

- What immune system cells are involved in the rejection of nonself transplants? **19-14**
- Why is a transplanted cornea usually not rejected as nonself? **19-15**
- Differentiate an embryonic stem cell from an adult stem cell. **19-16**
- Which type of transplant is most subject to hyperacute rejection? **19-17**
- When red bone marrow is transplanted, many immunocompetent cells are included. How can this be bad? **19-18**

Immunosuppression

To keep the problem of transplant rejection in perspective, it is useful to remember that the immune system is simply doing its job and has no way of recognizing that its attack against the transplant is not helpful. In an attempt to prevent rejection, the recipient of an allograft usually receives treatment to suppress this normal immune response against the graft.

In transplantation surgery, it is generally desirable to suppress cell-mediated immunity, the most important factor in transplant rejection. If humoral (antibody-based) immunity is not suppressed, much of the ability to resist microbial infection will remain. In 1976, the drug *cyclosporine* was isolated from a mold. The successful transplantation of organs such as hearts and livers generally dates from this discovery. Cyclosporine suppresses the secretion of interleukin-2 (IL-2), disrupting cell-mediated immunity by cytotoxic T cells. Following the success of this drug, other immunosuppressant drugs soon followed. *Tacrolimus* (FK506) has a mechanism similar to that of cyclosporine and is a frequent alternative, although both have many serious side effects. Neither cyclosporine nor tacrolimus has much effect on antibody production by the humoral immune system. Both of these drugs remain the mainstay for most regimens to prevent rejection of transplants. Some newer drugs, such as *sirolimus* (Rapamune), are among those that inhibit both cell-mediated and humoral immunity. This can be an advantage if chronic or hyperacute rejection by antibodies are a consideration. Sirolimus is best known for its use in stents, cylindrical meshes designed to keep blood vessels open after removal of blockages. Drugs such as mycophenolate inhibit the proliferation of T cells and B cells. Biological agents such as the chimeric monoclonal antibody (page 501) *basiliximab* (Simulect) block IL-2 and are frequently prescribed immunosuppressants. Immunosuppressive agents are usually administered in combinations.

Occasionally, a transplant recipient discontinues using immunosuppressant drugs but, surprisingly, does not reject the transplant. Research has provided an insight into a possible procedure to duplicate this deliberately. In these studies, a patient's immune system was treated before kidney transplantation surgery to deplete the body's supply of immune system T cells, which normally patrol for foreign invaders to attack. The transplanted tissue was then surgically implanted, along with bone marrow cells that had been harvested and stored before the patient's T cells were depleted. The subsequent results were unexpected: the immune system was rebuilt as a chimera—a hybrid mixture of the cells of the donated kidney and the patient's own cells. In consequence, the donated organ was accepted as self and not rejected. This retraining of the immune system often allows the patient to stop taking antirejection drugs less than a year after surgery.

Clinical Case

Lymphocytes originate from stem cells in the red bone marrow. From the red bone marrow the lymphocytes migrate to the thymus gland, where they mature into T cells. Malik was diagnosed with DiGeorge syndrome: a deletion in chromosome 22 that results in the underdevelopment or complete absence of the thymus gland. Malik, without an effective thymus, cannot develop T cells.

What is causing Malik's symptoms?

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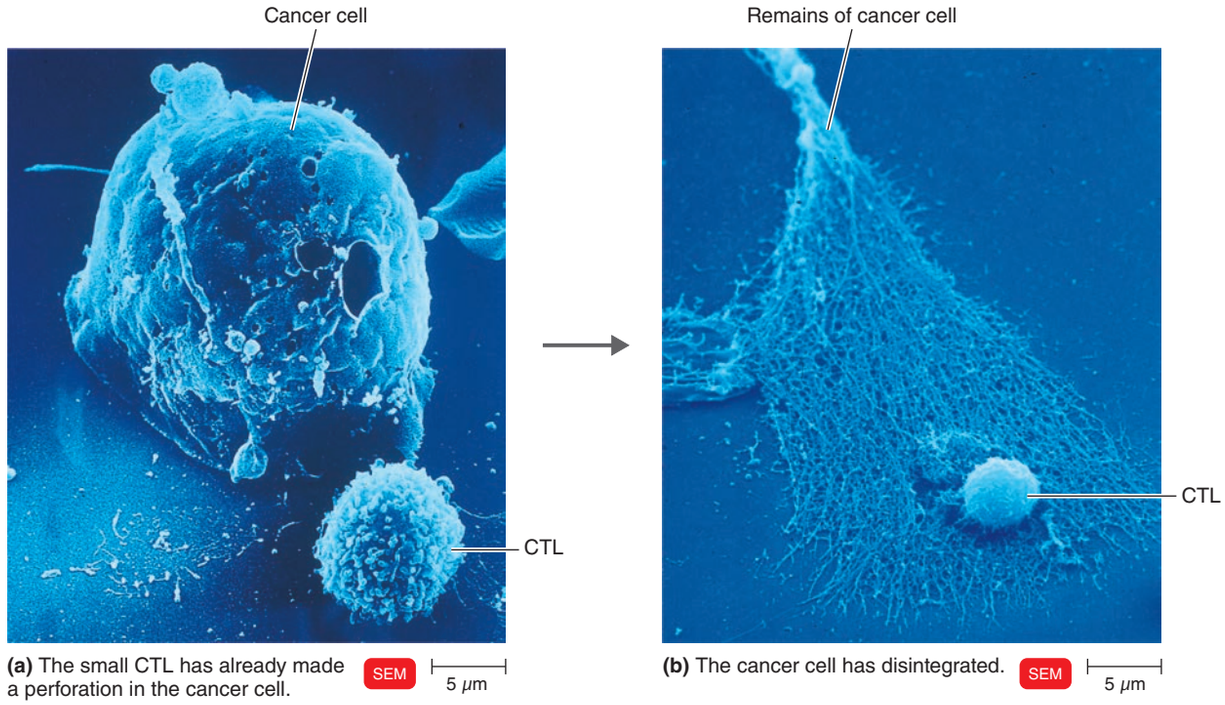


Figure 19.11 The interaction between a cytotoxic T lymphocyte (CTL) and a cancer cell.

Q CTLs can lyse cancer cells. How do they do this? (*Hint:* See Figure 17.14.)

A puzzling aspect is that the chimeric state is not permanent and the patient's immune system eventually returns to its original state—but still without rejecting the transplanted tissue. Carried to a logical extreme, this suggests the possibility of eventually using nonhuman organs as transplants.

CHECK YOUR UNDERSTANDING

✓ What cytokine is usually the target of immunosuppressant drugs intended to block transplant rejection? **19-19**

The Immune System and Cancer

LEARNING OBJECTIVES

19-20 Describe how the immune system responds to cancer and how cells evade immune responses.

19-21 Give two examples of immunotherapy.

Like an infectious disease, cancer represents a failure of the body's defenses, including the immune system. Some of the most promising avenues for effective cancer therapy make use of immunological techniques.

It has long been recognized that cancer cells arise frequently in the body and that they are usually eliminated by the immune system much like any other invading cell—the concept of **immune surveillance.** It was postulated that the cell-mediated immune system probably arose to combat cancer cells, and that the appearance of a cancerous growth represented a failure of the immune system. This concept has been supported by the observation that cancers occur most often in older adults, whose immune systems are becoming less efficient (called *immunosenescence*), or in the very young, whose immune systems may not have developed fully or properly. Also, individuals who are immunosuppressed by either natural or artificial means are more susceptible to certain cancers.

A cell becomes cancerous when it undergoes transformation and begins to proliferate without control (see Chapter 15, page 431). The surfaces of tumor cells acquire tumor-associated antigens that mark them as nonself to the immune system. Figure 19.11 illustrates the attack on such a cancer cell by activated T_C cells (cytotoxic T lymphocytes, or CTLs). Activated macrophages can also destroy cancer cells. Although a healthy immune system serves to prevent most cancers, it has limitations. In some cases there is no antigenic epitope for the immune system to target. Tumor cells can even reproduce so rapidly that they exceed the capacity of the immune system to deal with them. Finally, if the tumor cell begins reproducing in tissues and becomes vascularized (connected to the body's blood supply), it usually becomes invisible to the immune system.

Immunotherapy for Cancer

The hypothesis that cancer represents a failure of the immune system has led to the thought that the immune system might be used to prevent or cure cancer—that is, **immunotherapy.**

At the turn of the twentieth century, William B. Coley, a physician at a New York City hospital, observed that if cancer patients contracted typhoid fever, their cancers often diminished noticeably. Following this lead, Coley made mixtures of killed streptococci (gram-positive) and *Serratia marcescens* (gram-negative) bacteria. These so-called Coley's toxins were injected into cancer patients to simulate a bacterial infection. Some of this work was very promising, but its results were inconsistent, and advances in surgery and radiation treatment caused it to be nearly forgotten. It is now recognized that endotoxins from such bacteria are powerful stimulants for the production of tumor necrosis factor (TNF-α) by macrophages. TNF-α is a small protein that interferes with the blood supply of cancers in animals.

Other research determined many years ago that if animals were injected with dead tumor cells, as with a vaccine, they did not develop tumors when injected with live cells from these tumors. Similarly, cancers sometimes undergo spontaneous remission that is probably related to the immune system gaining the advantage. Treating or preventing cancer by immunological means will probably be an increasingly important approach. An attractive aspect is that this approach avoids the damage to healthy cells caused by chemotherapy and radiation treatments. Already, a vaccine for Marek's disease, a cancer of chickens, has been successful. Vaccines to protect cats from feline leukemia have also been shown to provide considerable protection.

Cancer vaccines might be either *therapeutic* (used to treat existing cancers) or *prophylactic* (to prevent the development of cancer). Prophylactic vaccines already exist; hepatitis B virus is a common cause of liver cancer, and a vaccine against infection by this virus is widely used. Also, a vaccine recommended for boys and girls ages 11–12, Gardasil, minimizes the chance of later development of cervical cancer caused by strains of a virus that also causes genital warts.

The world's first therapeutic cancer vaccine was approved by the FDA in 2010. Used to treat men with advanced prostate cancer, it is able to extend lives for only a few months—about the same as chemotherapy. However, it has fewer uncomfortable side effects and is considered to represent a proof of concept.

Monoclonal antibodies are a promising tool for delivering cancer treatment. A humanized monoclonal antibody, trastuzumab (*Herceptin*) (see Chapter 18, page 501), is currently being used to treat a form of breast cancer. Herceptin specifically neutralizes a genetically determined growth factor, HER2, that promotes the proliferation of the cancer cells. It is expressed in relatively high quantities in about 25–30% of breast cancer patients. Another approach is to combine a monoclonal antibody with a toxic agent, forming an **immunotoxin.** Theoretically, an immunotoxin might be used to specifically target and kill cells of a tumor with little damage to healthy cells. The FDA recently approved the drug Adcetris to treat Hodgkin's lymphoma. Adcetris is a conjugate of the monoclonal antibody brentuximab and an attached cytoxic drug (vedotin).

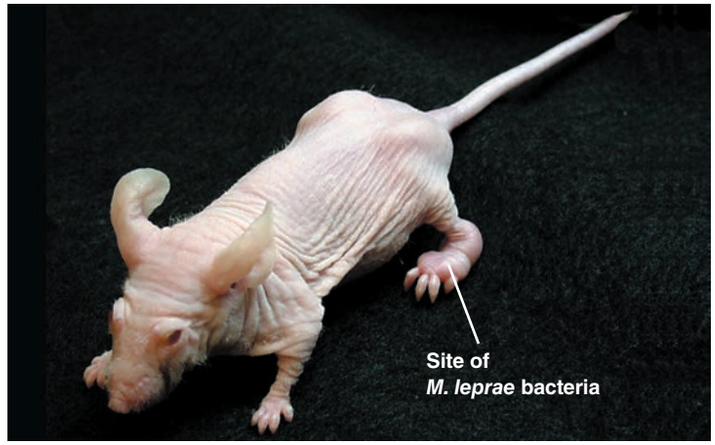


Figure 19.12 A nude (hairless) mouse infected with *Mycobacterium leprae* in the hind foot. Nude mice have no thymus and therefore no cell-mediated immunity. The immune response to infection by *M. leprae* (leprosy pathogen) depends on cell-mediated immunity, so these animals play an important role in leprosy research.

Q What is the role of the thymus gland in immunity?

CHECK YOUR UNDERSTANDING

- What is the function of tumor-associated antigens in the development of cancer? **19-20**
- Give an example of a prophylactic cancer vaccine that is in current use. **19-21**

Immunodeficiencies

LEARNING OBJECTIVE

19-22 Compare and contrast congenital and acquired immunodeficiencies.

The absence of a sufficient immune response is called an **immunodeficiency,** which can be either congenital or acquired.

Congenital Immunodeficiencies

Some people are born with a defective immune system. Defects in, or the absence of, a number of inherited genes can result in **congenital immunodeficiencies.** For example, individuals with a certain recessive trait, DiGeorge syndrome, do not have a thymus gland and therefore lack cell-mediated immunity. An animal equivalent, which is extremely valuable for research in transplantation science, is the nude (hairless) mouse (**Figure 19.12**). These mice have no thymus (the coincidental hairlessness is controlled by the same gene) and therefore do not produce T cells and do not reject transplanted tissue. Even chicken skin, complete with feathers, is readily accepted as a graft.

Acquired Immunodeficiencies

A variety of drugs, cancers, or infectious agents can result in **acquired immunodeficiencies.** For example, Hodgkin's lymphoma (a type of cancer) lowers the cell-mediated response.

TABLE 19.4 Immunodeficiencies

Disease	Cells Affected	Comments
Acquired immunodeficiency syndrome (AIDS)	Virus destroys $CD4^+$ T cells	Allows cancer and bacterial, viral, fungal, and protozoan diseases; caused by HIV infection
Selective IgA immunodeficiency	B, T cells	Affects about 1 in 700, causing frequent mucosal infections; specific cause uncertain
Common variable hypogammaglobulinemia	B, T cells (decreased immunoglobulins)	Frequent viral and bacterial infections; second most common immune deficiency, affecting about 1 in 70,000; inherited
Reticular dysgenesis	B, T, and stem cells (a combined immunodeficiency; deficiencies in B and T cells and neutrophils)	Usually fatal in early infancy; very rare; inherited; bone marrow transplant a possible treatment
Severe combined immunodeficiency	B, T, and stem cells (deficiency of both B and T cells)	Affects about 1 in 100,000; allows severe infections; inherited; treated with bone marrow and fetal thymus transplants; gene therapy treatment is promising
Thymic aplasia (DiGeorge syndrome)	T cells (defective thymus causes deficiency of T cells)	Absence of cell-mediated immunity; usually fatal in infancy from *Pneumocystis* pneumonia or viral or fungal infections; due to failure of the thymus to develop in embryo
Wiskott-Aldrich syndrome	B, T cells (few platelets in blood, abnormal T cells)	Frequent infections by viruses, fungi, protozoa; eczema, defective blood clotting; usually causes death in childhood; inherited on X chromosome
X-linked infantile (Bruton's) agammaglobulinemia	B cells (decreased immunoglobulins)	Frequent extracellular bacterial infections; affects about 1 in 200,000; the first immunodeficiency disorder recognized (1952); inherited on X chromosome

Many viruses are capable of infecting and killing lymphocytes, lowering the immune response. Removal of the spleen decreases humoral immunity. Table 19.4 summarizes several of the better known immune deficiency conditions, including AIDS.

Clinical Case

Without T cells, Malik lacks an effective immune system. The transfused blood contained immunologically competent lymphocytes, including T cells. A normal immune system would have neutralized these cells. In Malik's case, the transfused lymphocytes saw Malik as nonself and attacked his cells, meaning that he had developed graft-versus-host disease (GVHD). In this condition, the transfused T cells recognize and attack nonself cells in the new host. This recognition requires the T cells to attach to a T cell receptor and to a coreceptor such as CD3. When the T cell attaches to the receptor CD3 complex, it is stimulated to proliferate and attacks the antigen. A monoclonal antibody, muromonab-CD3 (Mab-CD3), is often used to treat immunological tissue rejection.

What role does the monoclonal antibody play in Malik's recovery? (Hint: See Chapter 18.)

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CHECK YOUR UNDERSTANDING

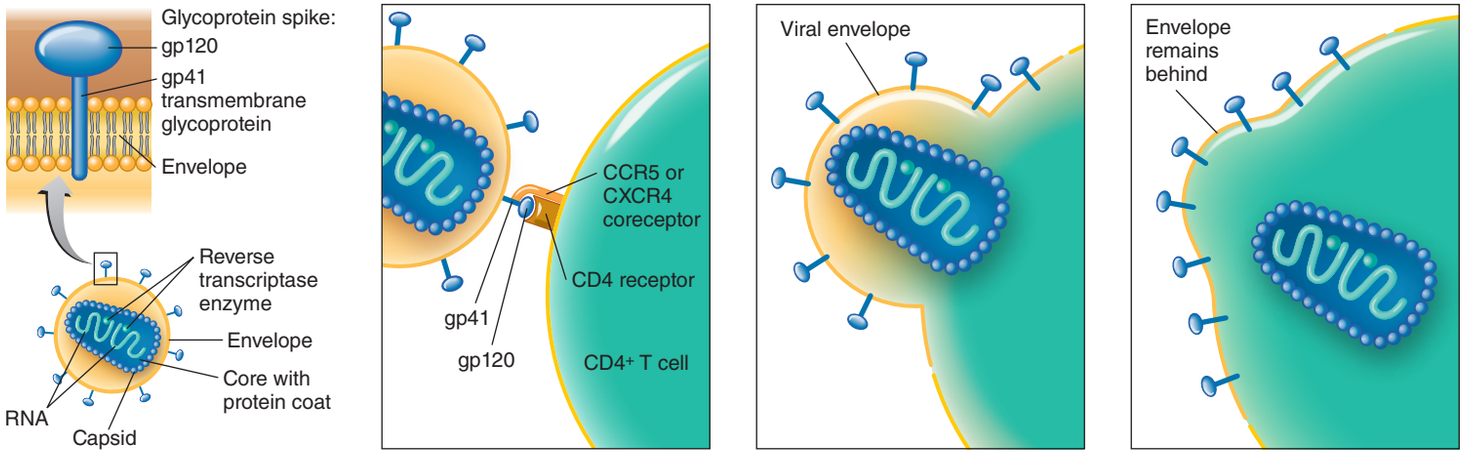
Is AIDS an acquired or a congenital immunodeficiency? 19-22

Acquired Immunodeficiency Syndrome (AIDS)

LEARNING OBJECTIVES

19-23 Give two examples of how infectious diseases emerge.
19-24 Explain the attachment of HIV to a host cell.
19-25 List two ways in which HIV avoids the host's antibodies.
19-26 Describe the stages of HIV infection.
19-27 Describe the effects of HIV infection on the immune system.
19-28 Describe how HIV infection is diagnosed.
19-29 List the routes of HIV transmission.
19-30 Identify geographic patterns of HIV transmission.
19-31 List the current methods of preventing and treating HIV infection.

In 1981, a cluster of cases of *Pneumocystis* pneumonia appeared in the Los Angeles area. Investigators soon correlated the appearance of this infrequently seen disease with an unusual incidence of a rare form of cancer of the skin and blood vessels called Kaposi's sarcoma. The people affected were all young homosexual men, and all showed a loss of immune function. By 1983, the pathogen causing the loss of immune function had



Structure of HIV and infection of a CD4⁺ T cell. The gp120 glycoprotein spike on the membrane attaches to a receptor on the CD4⁺ cell. The gp41 transmembrane glycoprotein probably facilitates fusion by attaching to a fusion receptor on the CD4⁺ cell.

1 **Attachment.** The gp120 spike attaches to a receptor and to a CCR5 or CXCR4 coreceptor on the cell.

2 **Fusion.** The gp41 participates in fusion of the HIV with the cell.

3 **Entry.** Following fusion with the cell, an entry pore is created. After entry, the viral envelope remains behind and the HIV uncoats, releasing the RNA core for directing synthesis of the new viruses.

Figure 19.13 HIV structure and attachment to receptors on target T cell.

Q Why does HIV preferentially infect CD4⁺ cells?

been identified as a virus that selectively infects T helper cells. This virus is now known as human immunodeficiency virus, or HIV (see Figure 1.1e, page 5).

The Origin of AIDS

HIV is now believed to have arisen by the mutation of a virus that had been endemic in wildlife in some areas of Africa. HIV-2, a type of HIV that is weakly contagious and not often found outside west Africa, is a mutation of a simian immunodeficiency virus (SIV). Mangabey monkeys in west Africa are naturally and harmlessly infected with this SIV. More recently, studies show that HIV-1 (the primary HIV found worldwide in humans) is genetically related to another SIV that is carried by chimpanzees in central Africa.

However, HIV-1 had probably been spreading among the human population of west and central Africa long before **AIDS** (the final stage of an HIV infection) was identified as a disease. SIV infections in animals had apparently crossed over into the human population known to eat wild nongame animals called bushmeat. It is now considered probable that this transfer from chimpanzees to humans occurred around 1908. The disease may have smoldered with little notice as long as transmission was limited to small villages, where rates of sexual promiscuity were low. The virus could not have killed or incapacitated its hosts quickly; otherwise, it could not have been maintained in the village population. With the sudden end of European colonialism, the social structure of sub-Saharan Africa became urbanized, a change that was associated with increased sexual promiscuity—especially an increase in prostitution—and the growth of transportation. The earliest documented case of AIDS is that of a patient in Leopoldville, Belgian Congo (now Kinshasa, Democratic Republic of the Congo). This man died in 1959, and preserved samples of the blood contain antibodies to HIV. In the Western world, the first confirmed case of AIDS was the death of a Norwegian sailor in 1976, who probably was infected in 1961 or 1962 by contacts in western Africa.

CHECK YOUR UNDERSTANDING

On what continent did the HIV-1 virus arise? **19-23**

HIV Infection

The Structure of HIV

HIV, of the genus *Lentivirus,* is a retrovirus (see Figure 13.19, page 379). It has two identical strands of RNA, the enzyme reverse transcriptase, and an envelope of phospholipid (**Figure 19.13**). The envelope has glycoprotein spikes termed **gp120** (the notation for a glycoprotein with a molecular weight of 120,000).

The Infectiveness and Pathogenicity of HIV

There is a strong association between HIV infection and the immune system. HIV is often spread by dendritic cells, which pick up the virus and carry it to the lymphoid organs. There it contacts cells of the immune system, most notably activated T cells, and stimulates an initial strong immune response.

To be infective, HIV must go through the steps of attachment, fusion, and entry in a manner similar to that shown in Figure 19.13.

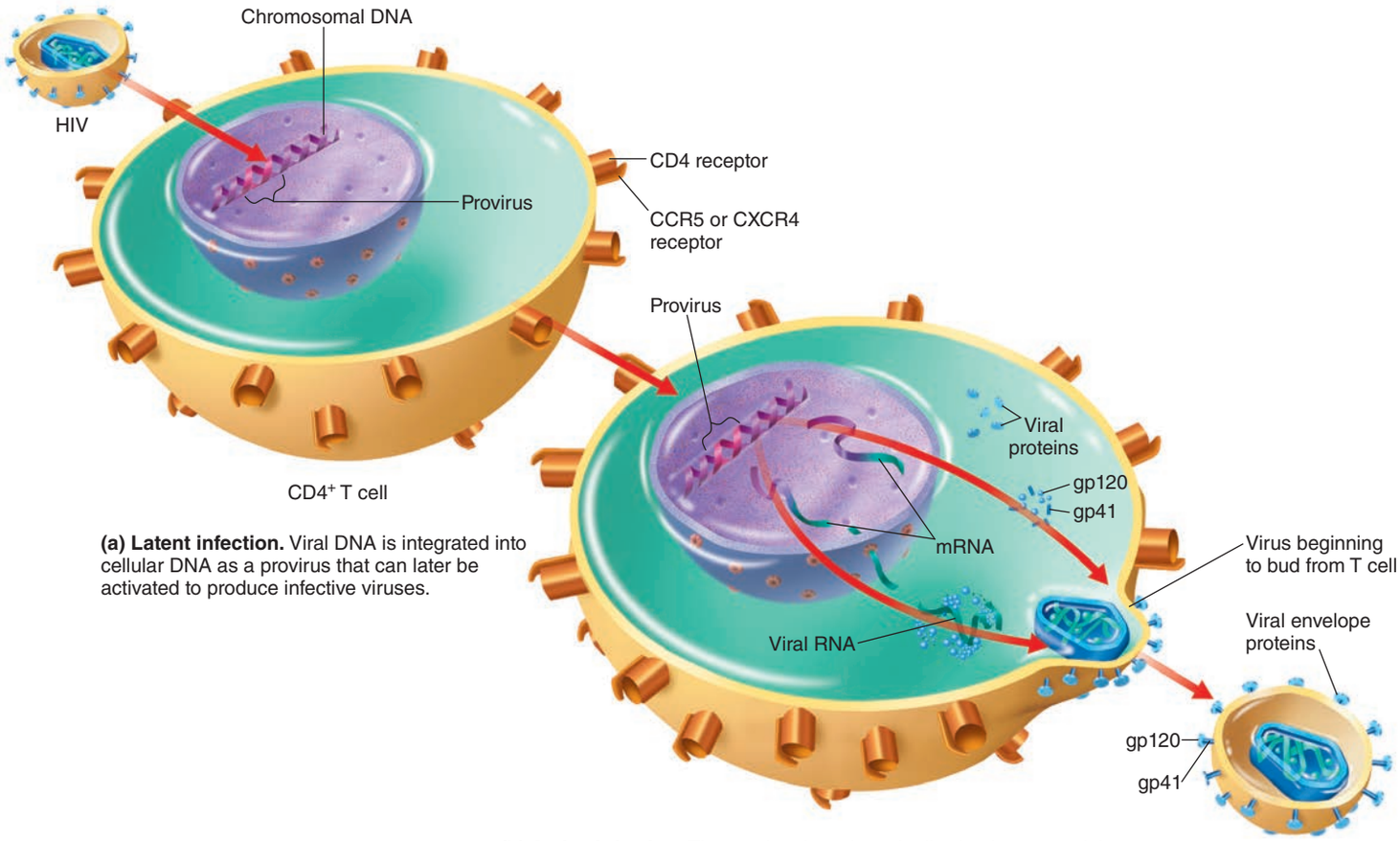


Figure 19.14 Latent and active HIV infection in CD4$^+$ T cells.

Q What is a latent infection?

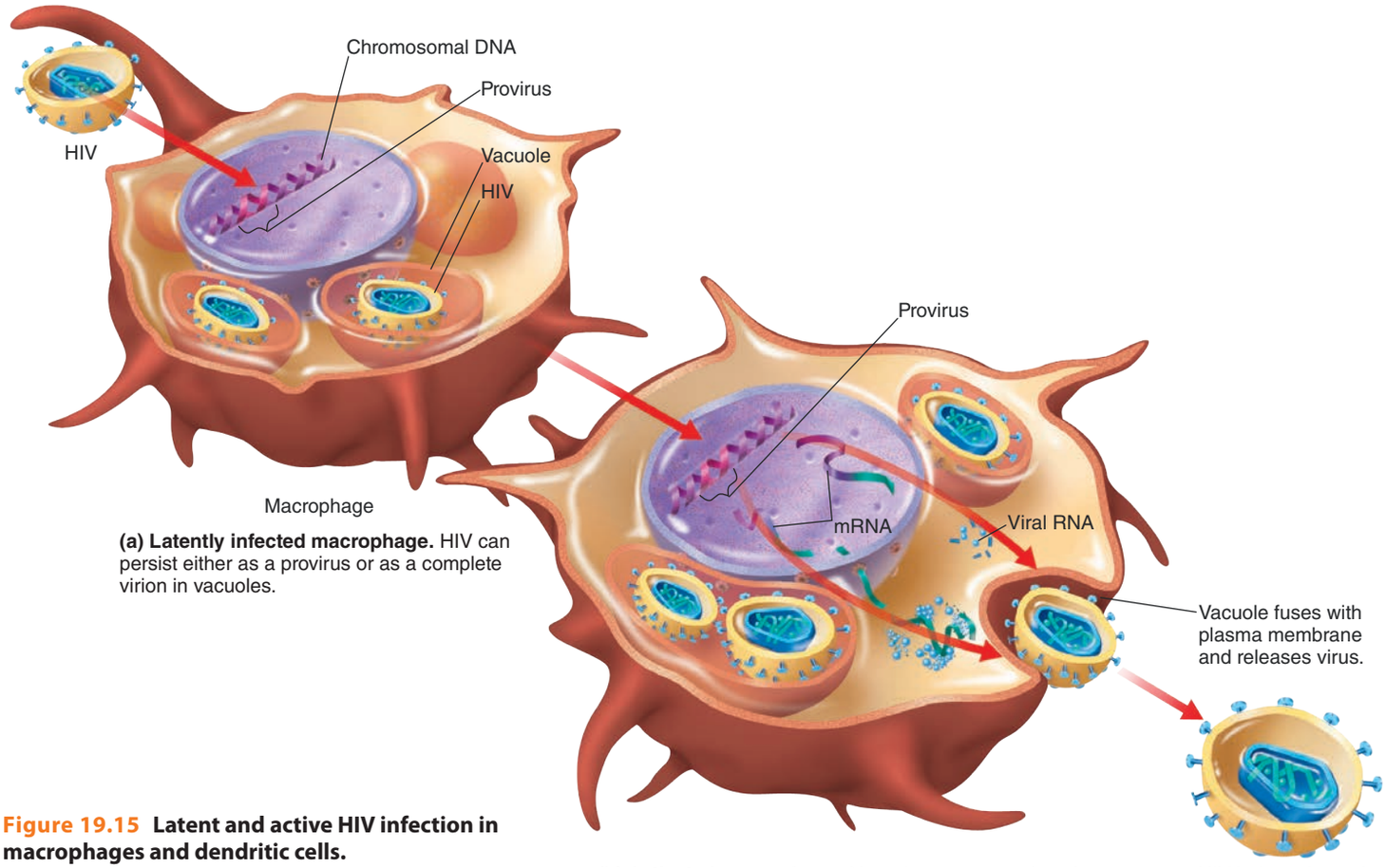
Attachment to the target cell depends on the glycoprotein spike (gp120) combining with the CD4$^+$ receptor. Approximately 65,000 of these receptors are found on each CD4$^+$ T helper cell, which is the main target of HIV infection. Certain coreceptors are also required. The two best-known chemokine coreceptors are named CCR5 and CXCR4.* Macrophages and dendritic cells also carry CD4 molecules. (Many cells that do not express the CD4 molecule can also become infected, an indication that other receptors can also serve for infection by HIV.)

In the host cell, viral RNA is released and transcribed into DNA by the enzyme reverse transcriptase. This viral DNA then becomes integrated into the chromosomal DNA of the host cell. The DNA may control the production of an active infection in which new viruses bud from the host cell, as shown in **Figure 19.14b**.

Alternatively, this integrated DNA may not produce new HIV, but may remain hidden in the host cell's chromosome as a *provirus* (Figure 19.14a and **Figure 19.15a**). HIV produced by a host cell is not necessarily released from the cell but may remain as *latent virions* in vacuoles within the cell (Figure 19.15b). In fact, a subset of the HIV-infected cells, instead of being killed, become long-lived memory T cells in which the reservoir of latent HIV can persist for decades. This ability of the virus to remain as a provirus or latent virus within host cells shelters it from the immune system. Another way HIV evades the immune system is *cell–cell fusion,* by which the virus moves from an infected cell to an adjacent uninfected cell.

The virus also evades immune defenses by undergoing rapid antigenic changes. Retroviruses, with the reverse transcriptase enzyme step, have a high mutation rate compared to DNA viruses. They also lack the corrective "proofreading" capacity of DNA viruses. As a result, a mutation is probably introduced at every position in the HIV genome many times each day in an infected person. This may amount to an accumulation

*This nomenclature is based on the beginning amino acid sequence in these proteins. The term CCR5 indicates that the beginning sequence consists of cysteines, thus CC. The letter R is a convention representing the balance of the protein molecule, and the number is for identification. If some other amino acid is located between the first two cysteines, this is shown in the naming—for example, CXCR4.



(a) Latently infected macrophage. HIV can persist either as a provirus or as a complete virion in vacuoles.

(b) Activated macrophage. New viruses are produced from provirus. Completed virions are either released or persist in the macrophage within vacuoles.

Figure 19.15 Latent and active HIV infection in macrophages and dendritic cells.

Q How does an active infection differ from a latent infection?

of 1 million variants of the virus in an asymptomatic person and 100 million variants during the final stages of the infection. These dramatic numbers illustrate the potential problems of drug resistance and obstacles to the development of vaccines and diagnostic tests.

Subtypes of HIV

Worldwide, the highly variable genome of HIV has separated into distinctive groups. There are two major types, HIV-1 and HIV-2. The most seriously pathogenic is HIV-1, which accounts for about 99% of cases. It is related to viruses found in western Africa that infect primates such as chimpanzees and gorillas. HIV-1 viruses are further subdivided into groups that are assigned letter combinations. Group M (for "majority") accounts for about 90% of cases. Naming conventions become further complicated with lettered subtypes. For example, HIV-1 group M, subtype B is the main variety of HIV found in Europe. Australia, Japan, and the Americas.

HIV-2 is related to a virus endemic in a species of monkeys, the sooty mangabeys, found in west Africa. This strain is not often encountered outside Africa. It is less pathogenic than HIV-1, and people who contract this infection often live asymptomatically for extended periods of time.

The Stages of HIV Infection

The progress of HIV infection in adults can be divided into three clinical phases (**Figure 19.16**):

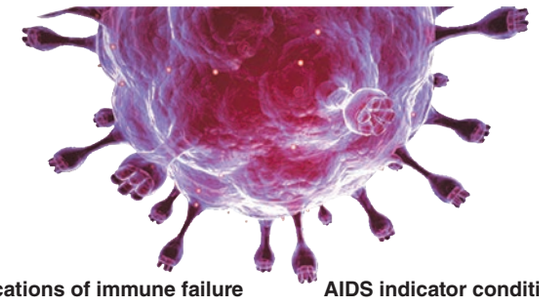
Phase 1 The number of viral RNA molecules per milliliter of blood plasma may reach more than 10 million in the first week or so. Billions of $CD4^+$ T cells may be infected within a couple of weeks. Immune responses and fewer uninfected cells to target deplete viral numbers in blood plasma sharply within a few weeks. The infection may be asymptomatic or cause *lymphadenopathy* (swollen lymph nodes).

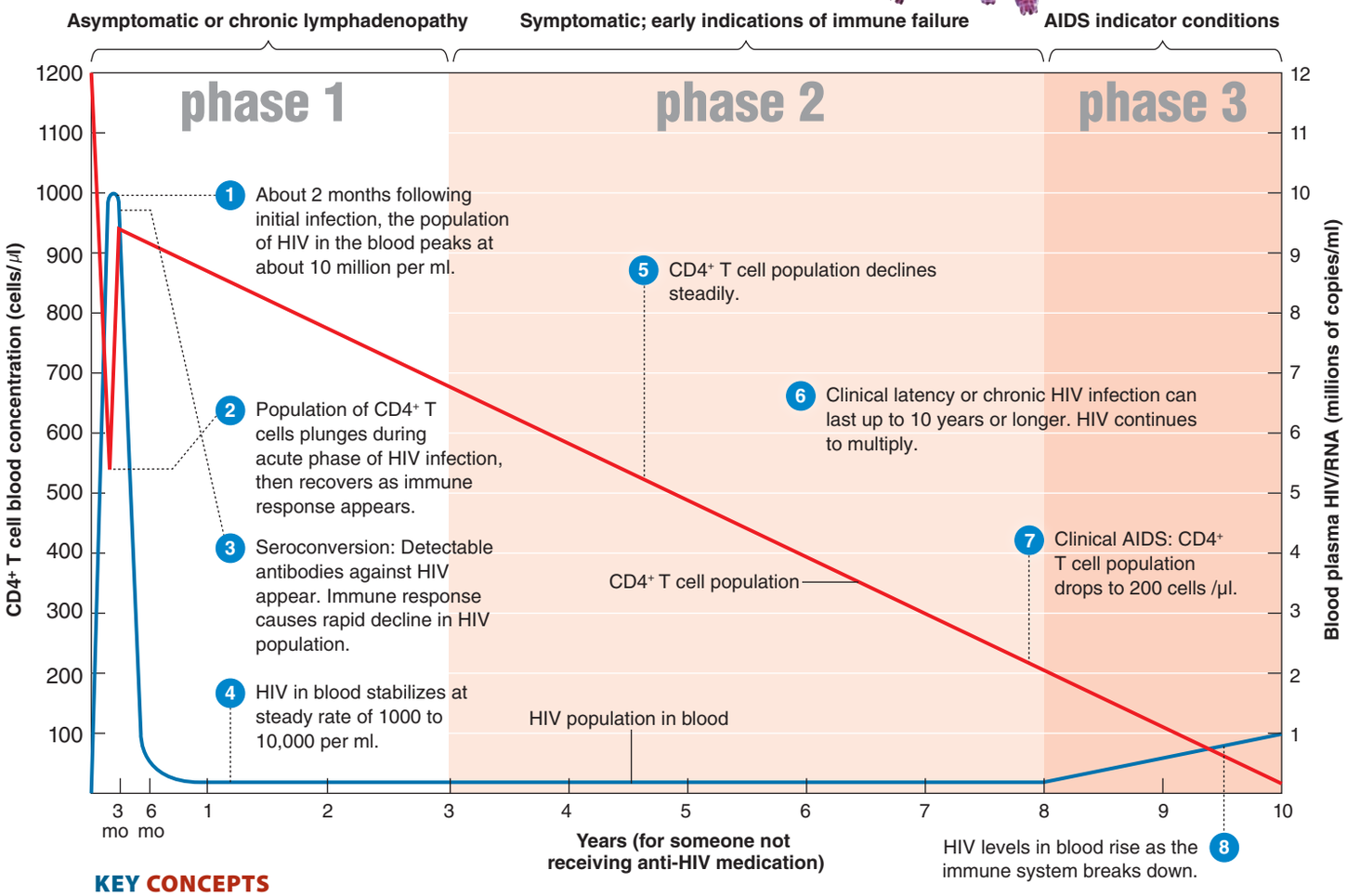
Phase 2 The numbers of $CD4^+$ T cells decline steadily. HIV replication continues but at a relatively low level, probably controlled by $CD8^+$ T cells (see page 483 in Chapter 17) and occurs mainly in lymphatic tissue. Only a relatively few infected cells release HIV, although many may contain viruses in latent or proviral form. There are few serious disease symptoms, but

FOUNDATION FIGURE 19.16

The Progression of HIV Infection

Understanding how the HIV infection progresses in a host is integral to understanding the diagnosis, transmission, and prevention of this pandemic. Although there is no cure, see information below on drug treatments.





KEY CONCEPTS

- HIV progresses as it destroys the CD4+ T cells essential for the body's defenses against infectious disease and cancer.
- AIDS is the final stage in this progressive infection.

micro tip

Although there is no cure for HIV, combinations of anti-HIV medications (antiretroviral therapy) are the recommended treatment. Individuals undergoing treatment can still transmit the disease. The medications work in a variety of ways: disabling or stopping proteins from making more copies of HIV, disrupting building blocks needed for viral replication, or blocking entry of the virus into cells. •

a decline in immune response may become apparent by the appearance of persistent infections by the yeast *Candida albicans,* which can appear in the mouth, throat, or vagina. Other conditions may include fever and persistent diarrhea. Oral leukoplakia (whitish patches on oral mucosa), which results from reactivation of latent Epstein-Barr viruses, may appear, as well as other indications of declining immunity, such as shingles.

Phase 3 One of the most common misconceptions is that HIV infection is synonymous with AIDS. AIDS denotes only the final phase. In clinical AIDS, $CD4^+$ T cell counts are below 200 cells/μl. Important AIDS indicator conditions appear, such as *C. albicans* infections of bronchi, trachea, or lungs; cytomegalovirus eye infections; tuberculosis; *Pneumocystis* pneumonia; toxoplasmosis of the brain; and Kaposi's sarcoma.

The Centers for Disease Control and Prevention (CDC) classifies the progress of HIV infections based on T cell populations. The purpose is primarily to furnish guidance for treatment, such as when to administer certain drugs. The normal population of a healthy individual is 800 to 1000 $CD4^+$ T cells/μl. In the United States, a count below 350 cells/μ1 is an indicator for initiating therapy with retroviral drugs.

The progression from initial HIV infection to AIDS usually takes about 10 years in adults in industrialized countries; in Africa, it is often about half this. Cellular warfare on an immense scale occurs during this time. At least 100 billion HIVs are generated every day, each with a remarkably short half-life of about 6 hours. These viruses must be cleared by the body's defenses, which include antibodies, CTLs, and macrophages. Almost all HIVs, at least 99%, are produced by infected $CD4^+$ T cells, which survive for only about 2 days (T cells normally live for several years). Every day, an average of about 2 billion $CD4^+$ T cells are produced in an attempt to compensate for losses. Over time, however, there is a daily net loss of at least 20 million $CD4^+$ T cells, one of the main markers for the progression of HIV infection. The most recent studies show that the decrease in $CD4^+$ T cells is not due entirely to direct viral destruction of the cells; rather, it is caused primarily by shortened life of the cells and the body's failure to compensate by increasing production of replacement T cells.

Resistance to HIV Infection

A feature of HIV infection is that the virus proliferates despite efforts of the humoral and cellular immune systems. HIV infection stimulates an initial strong and fairly effective immune response in the first and second phases of infection. A few months after infection, virus levels decline greatly. The most important factor in this is probably CTLs ($CD8^+$ T cells). Neutralizing antibodies do not emerge until the viremia has passed its peak and rapid genetic changes in the virus lower the effectiveness of antibodies, but CTLs continue to suppress viral numbers. However, once HIV establishes a pool of latently infected $CD4^+$ T cells, almost no patients completely clear the infection. This reservoir is not eradicated even when antiviral therapy reduces the viremia to undetectable levels (less than 50 viruses per milliliter). The establishment of a latent infection contrasts with almost all other viral infections and is a challenge to any vaccine.

Impact of Age on Survival with HIV Infection

The age of the infected person can also be an important factor in survival. Older adults are less able to replace $CD4^+$ T cell populations. Infants and younger children have an immune system that is not fully developed, leaving them much more susceptible to opportunistic infections.

Infants born to HIV-positive mothers are not always infected—in fact, only about 20% are. Infants who are most seriously infected survive less than 18 months.

HIV infection devastates the immune system, which is then unable to respond effectively to pathogens. The diseases or conditions most commonly associated with HIV infection and AIDS are summarized in **Table 19.5**. Success in treating these conditions has extended the lives of many HIV-infected people.

Exposed, But Not Infected, Population Certain high-risk people are repeatedly exposed to HIV but remain free of infection. HIV primarily enters cells by first attaching to the CD4 receptor and then binding to coreceptors such as CCR5. About 1–3% of the populations of the Western world do not have a gene for CCR5 and are, therefore, highly resistant to HIV infections.

The role of CCR5 in natural resistance has led to research into drugs that block the receptor.

Experiments are under way for the use of gene therapy to treat AIDS by replacing the patient's T-cell population with T cells that are not susceptible to infection. The initial step is to remove some T cells from patients and modify them by deleting their CCR5. These populations of modified cells would then be multiplied and infused back into the patients. In the small group of patients in which this is being tested, there is encouraging evidence that the numbers of these modified cells are slowly increasing in the patient's bloodstream.

Long-Term Survivors Occasionally, certain therapeutically untreated individuals who have been infected with HIV for more than 10 years have not progressed to AIDS. These people are called *long-term nonprogressors*. Other individuals who are repeatedly infected with the virus never progress to AIDS and have little to no virus in their blood. They are called *elite controllers*.

It has been established now that these individuals have CTLs with unusual powers that are capable of destroying fast-mutating viruses such as HIV. These long-term survivors are of exceptional interest because they might provide insights into treatments for all HIV-infected persons.

TABLE 19.5 Some Diseases Commonly Associated with AIDS

Pathogen or Disease	Disease Description
PROTOZOA	
Cryptosporidium hominis	Persistent diarrhea
Toxoplasma gondii	Encephalitis
Isospora belli	Gastroenteritis
VIRUSES	
Cytomegalovirus	Fever, encephalitis, blindness
Herpes simplex virus	Vesicles of skin and mucous membranes
Varicella-zoster virus	Shingles
BACTERIA	
Mycobacterium tuberculosis	Tuberculosis
M. avium-intracellulare	May infect many organs; gastroenteritis and other highly variable symptoms
FUNGI	
Pneumocystis jirovecii	Life-threatening pneumonia
Histoplasma capsulatum	Disseminated infection
Cryptococcus neoformans	Disseminated, but especially meningitis
Candida albicans	Overgrowth on oral and vaginal mucous membranes (phase 2 stage of HIV infection)
C. albicans	Overgrowth in esophagus, lungs (phase 3 stage of HIV infection)
CANCERS OR PRECANCEROUS CONDITIONS	
Kaposi's sarcoma	Cancer of skin and blood vessels (caused by human herpesvirus 8)
Hairy leukoplakia	Whitish patches on mucous membranes; commonly considered precancerous
Cervical dysplasia	Abnormal cervical growth

CHECK YOUR UNDERSTANDING

- What is the primary receptor on host cells to which HIV attaches? **19-24**
- Would an antibody against the coat of HIV be able to react with a provirus? **19-25**
- Would a $CD4^+$ T cell count of 300/μl be diagnostic of AIDS? **19-26**
- Which cells of the immune system are the main target of an HIV infection? **19-27**

Diagnostic Methods

The CDC now recommends routine screening for HIV infections in several circumstances, especially in patients beginning treatment for tuberculosis and in patients seeking treatment for sexually transmitted infections. The standard procedure for detecting HIV antibodies has been an ELISA test (see Figure 18.14, page 510). There are now several relatively inexpensive, rapid tests available for HIV screening that are especially useful at urgent care clinics and emergency departments, as well as in developing, resource-poor countries. The tests use urine or fingerstick amounts of blood, and the OraQuick test can even use an oral swab of fluid to check for HIV antibodies. They return results in 10 to 20 minutes, and some can potentially be used for home testing. An estimated 25% of HIV-positive Americans do not realize they are infected; this lack of knowledge fuels the spread of the disease. Inexpensive, rapid routine screening tests should be valuable in changing this.

Positive screening tests for antibodies must be confirmed by additional testing, usually by the Western blot test (see Figure 10.12, page 279).

A problem with antibody-type testing is the window of time between infection and the appearance of detectable antibodies, or **seroconversion.** This interval, which can be as long as 3 months, is illustrated in step 3 of Figure 19.16, where seroconversion follows the peak number of viruses in circulation. Because of this delay, the recipient of an organ transplant or a blood transfusion can become infected with HIV even though antibody tests did not show the presence of the virus in the donor. Improvements in testing have gradually narrowed the window to 21 to 25 days.

An alternative to the Western blot confirmatory test has received FDA approval. Instead of antibodies, the APTIMA assay detects the RNA of the HIV-1 virus using real-time PCR, and it is easier to read than the Western blot test. This test can also be used to detect early HIV infections, before appearance of antibodies. Its sensitivity is comparable to tests used to measure **plasma viral load (PVL)** in the blood of patients to monitor the treatment and progression of AIDS. Conventional PVL tests that detect viral RNA use methods such as PCR or nucleic acid hybridization, are costly, and require 2 or 3 days to complete.

Viral RNA can be detected in 7 to 10 days and, less reliably, in 2 to 4 days. To ensure safety of the blood supply as much as possible, the American Red Cross has introduced testing for anti-HIV antibody and nucleic acid hybridization testing for viral HIV (see the box on page 730).

Tests that detect viral RNA are the only option during the primary infection, before antibodies appear, and in infants of HIV-infected mothers who have circulating maternal antibodies that interfere with conventional tests to detect antibodies.

A caution to keep in mind in testing for HIV is that current tests may not reliably detect all of the myriad variants of rapidly mutating HIV, especially subtypes that are not normally present in a population. Furthermore, PVL tests sample only the virions circulating in the blood, which is very low compared to the estimated several hundred billion HIV-infected cells.

CHECK YOUR UNDERSTANDING

What form of nucleic acid is detected in a PVL test for HIV? **19-28**

HIV Transmission

The transmission of HIV requires the transfer of, or direct contact with, infected body fluids. The most important of these is blood, which contains 1000 to 100,000 infective viruses per milliliter, and semen, which contains about 10 to 50 viruses per milliliter. The viruses are often located within cells in these fluids, especially in macrophages. HIV can survive more than 1.5 days inside a cell but only about 6 hours outside a cell. Saliva generally contains less than 1 virus per milliliter, and kissing is not known to transmit HIV. In developed countries, transmission by transfusion is unlikely because blood is tested for HIV or HIV antibodies.

Routes of HIV transmission include intimate sexual contact, breast milk, transplacental infection of a fetus, blood-contaminated needles, organ transplants, artificial insemination, and blood transfusion. The risk of infection from needlestick injury is 3 out of 1000, or 0.3%. Avoiding exposure is the health care worker's first line of defense against HIV. The CDC has developed the strategy of following *universal precautions* in *all* health care settings.

Probably the most dangerous form of sexual contact is anal-receptive intercourse. These tissues are much more vulnerable to transmission of disease organisms. Vaginal intercourse is much more likely to transmit HIV from man to woman than vice versa, and transmission either way is much greater when genital lesions are present. Although rare, transmission can occur by oral-genital contact.

CHECK YOUR UNDERSTANDING

What is considered to be the most dangerous form of sexual contact for transmission of HIV? **19-29**

AIDS Worldwide

Approximately 35 million people are infected with, and living with, HIV today (**Figure 19.17**). An estimated 70% of these are in sub-Saharan Africa, including nearly 90% of the world's HIV-infected children. South and southeast Asia, with their dense populations, also have a high number of cases, an estimated 3.5 million. As the disease becomes established in the huge populations of China and India, the incidence of HIV could exceed more than 1 million new cases a year. Eastern Europe, Russia, and central Asia are also areas reporting a steep rise in HIV infections. In western Europe and the United States, the mortality from AIDS has decreased because of the availability of effective antiviral drugs (see Figure 14.4, on page 396).

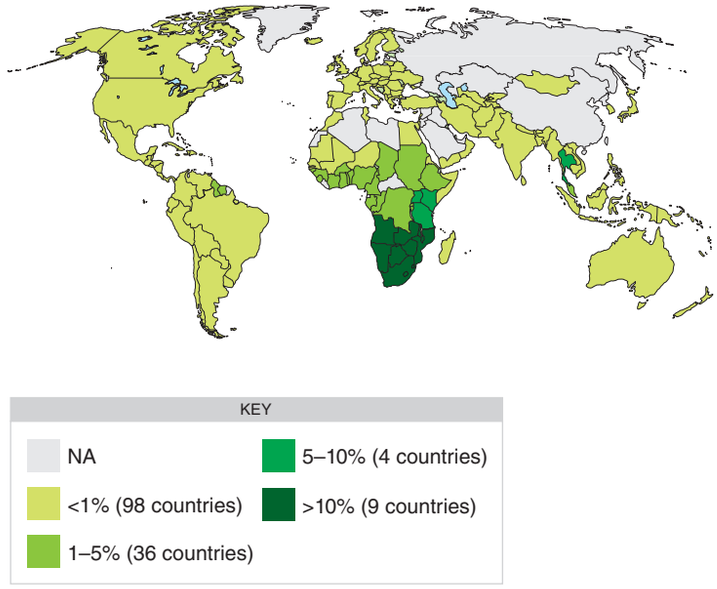


Figure 19.17 Distribution of HIV infection and AIDS in regions of the world. Shows percentage of adults (15-49) living with HIV/AIDS.

Q Where do you think the most accurate figures would be available?

Early in the HIV/AIDS pandemic, transmission in the United States and Europe was most commonly by male homosexual activity and with the use of injected drugs. These factors are still very important in the Western world, particularly in North and South America and Europe. Currently, one-third of all HIV infections in eastern Europe and central and southeast Asia are by use of injected drugs. These infections are also important as a bridge leading to other forms of transmission. Worldwide, heterosexual transmission is predominant (about 85%), especially in the less developed parts of the world, such as the center of the pandemic in sub-Saharan Africa. A feature of the pandemic in recent times has been the increasing percentage of women infected (about 42% worldwide, most living in sub-Saharan Africa), with associated mother-to-child transmission. Most of these cases are young women infected by older men.

CHECK YOUR UNDERSTANDING

What is the most common mode, worldwide, by which HIV is transmitted? **19-30**

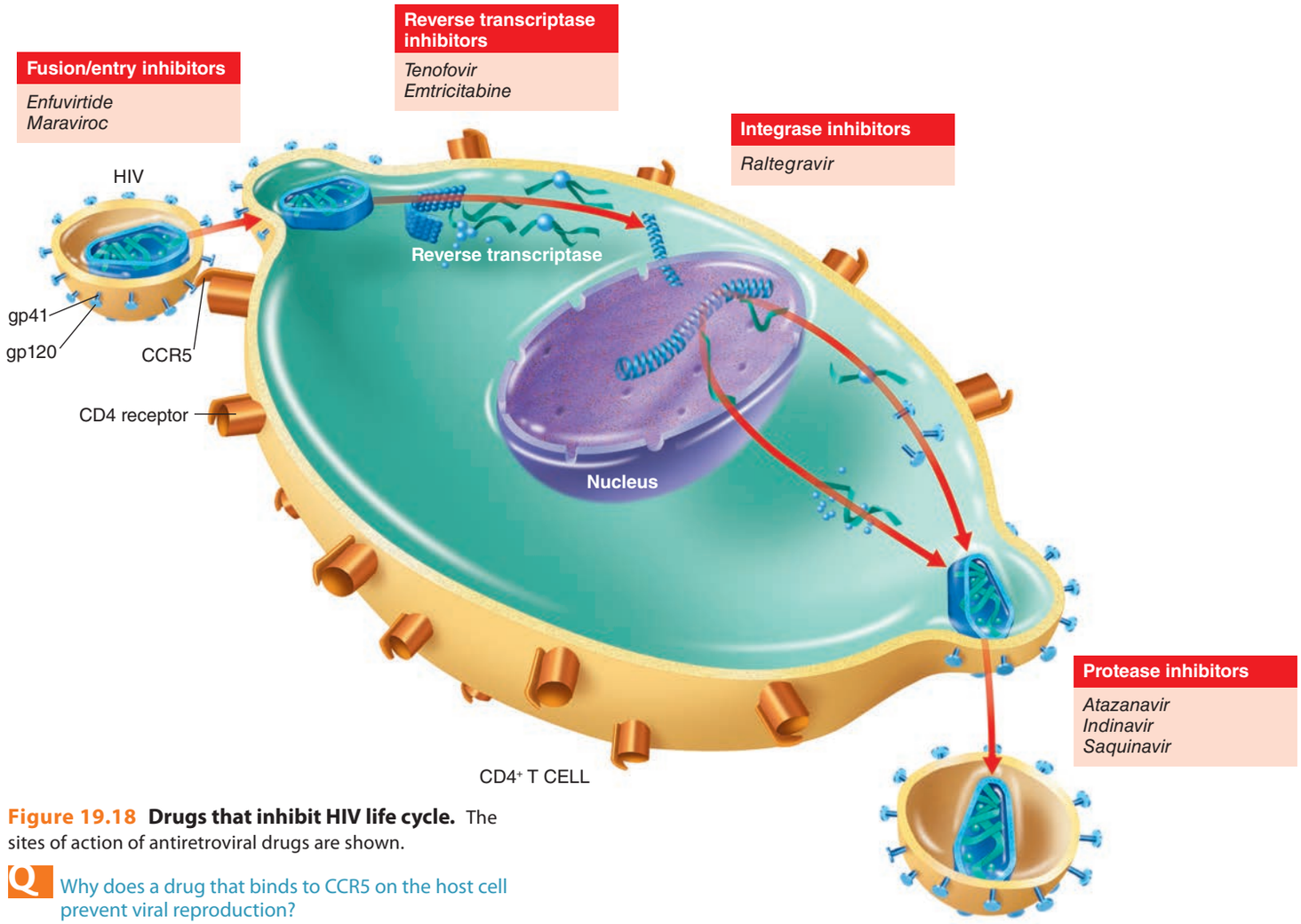


Figure 19.18 Drugs that inhibit HIV life cycle. The sites of action of antiretroviral drugs are shown.

Q Why does a drug that binds to CCR5 on the host cell prevent viral reproduction?

Preventing and Treating AIDS

At present, for most of the world the only practical means of control is to minimize transmission. This requires educational programs to promote the use of condoms, as well as discouraging sexual promiscuity. In certain cultures, especially sub-Saharan Africa, women are frequently sexually exposed to HIV and have very limited control. It is hoped that a vaginal gel containing an effective microbicide (cell entry inhibitors) will become widely available.

In underdeveloped countries, contaminated blood is a common source of infection, and programs are needed to encourage the use of only sterile needles. Injecting drug users tend to have a high rate of HIV infections. Hospitals in underdeveloped countries must reuse needles for economic reasons, and resterilization is difficult.

In developed countries, the availability of medication has changed HIV from an almost certainly fatal disease into a chronic disease. But drug therapies are not a cure. Also, these improvements in managing HIV infection have unfortunately resulted in a relaxed attitude toward safer-sex practices, which has offset some value of the treatments.

Chemotherapy

Because of the increasing number of drugs that at least temporarily control reproduction of the virus, HIV infection can now be considered a treatable chronic disease in the developed world. (Accessibility and affordability of HIV treatments continue to be a challenge in developing nations.) Major obstacles to treating HIV, as with developing a vaccine, are the high mutation rate that quickly leads to resistant strains and the persistence of latent viral reservoirs. If the effective drugs are interrupted or discontinued, the virus rebounds rapidly. Research into the reproductive mechanisms of HIV has increased the number of potential targets for chemical intervention. **Figure 19.18** shows the major types of drugs available.

Fusion/Cell Entry Inhibitors An obvious target for anti-HIV is the entry of the virus into the cell. For infection to occur, the virus

must attach to the cell's CD4 receptors; an interplay between the gp120 spike on the virus and the coreceptor (such as CCR5) must occur; and finally, there must be a *fusion* with the cell to allow viral entry. Drugs to block these steps are grouped as *cell entry inhibitors;* some of the newer drugs of this group target the gp41 region of the viral envelope, which facilitates fusion. An example is *enfuvirtide,* which is expensive and requires daily injections. Another cell entry inhibitor is *maraviroc,* which blocks the chemokine receptor CCR5 to which HIV must bind.

Reverse Transcriptase Inhibitors The first target of anti-HIV drugs was the enzyme reverse transcriptase, an enzyme not present in human cells. In fact, the term **antiretroviral** currently implies that a drug is used to treat HIV infections. These *nucleoside reverse transcriptase inhibitors (NRTIs)* are analogs of nucleosides and cause the termination of viral DNA by competitive inhibition. There are other drugs that inhibit reverse transcription but are not analogs of nucleic acids; these are the so-called *nonnucleoside reverse transcriptase inhibitors (NNRTIs).* The rapid reproductive rate and frequent occurrence of drug-resistant mutations dictates that multiple drugs, given simultaneously, must be used. The current treatment is termed **highly active antiretroviral therapy (HAART).** This therapy consists of administering drug combinations. Patients are often required to take as many as 40 pills a day on a complex schedule. Even so, resistant strains of the virus are likely to emerge. The majority of AIDS patients in the United States receive multiple-drug therapy to minimize survival of resistant strains. The drugs are commonly combined in a single pill to simplify administration. Examples are Truvada, a combination of *tenofovir* and *emtricitabine* (both NRTIs); and Atripla, a combination of these two drugs plus *efavirenz* (an NNRTI). Experience has also shown that eliminating all viruses in latent form in lymphoid tissue is especially difficult. The number of HIV in circulation is often reduced to fewer than can be detected, but this is not the same as eradication.

Integrase Inhibitors After fusion has been completed, reverse transcription from the RNA genome produces a double-stranded cDNA version of HIV, which enters the nucleus. Within the nucleus, the complex containing the cDNA must be integrated into the host chromosome to form the HIV provirus. This step requires an enzyme, HIV integrase, which is a target for drugs called *integrase inhibitors*. *Raltegravir* is an example.

Protease Inhibitors A second enzymatic target of HIV is proteases. Proteases perform the essential process of cleaving lengthy viral precursor proteins into smaller, mature structural proteins (such as the capsid proteins) and functional proteins (such as essential enzymes). Most of this occurs as the virus is budding from the cell membrane and shortly thereafter. *Protease inhibitor* drugs such as *atazanavir, indinavir,* and *saquinavir* have proved especially effective when combined with inhibitors of reverse transcriptase.

There are several other targets for which drugs are being developed. For example, some **maturation inhibitors** affect the conversion of a precursor of capsid protein to mature capsid protein, resulting in an aberrant capsid that renders the virus noninfectious. Other potential drugs are **tetherins,** which tether the newly formed virus to the cell, preventing its release and spread. Research will probably reveal new targets and chemotherapeutic agents affecting them. Especially important is the need to find drugs that can eradicate the virus in its latent reservoirs. One clearly successful application of chemotherapy has been to reduce the chance of HIV transmission from an infected mother to her newborn. The administration of even one NRTI drug alone greatly reduces the incidence. Another promising application of chemotherapy is the current African trials of a vaginal gel containing tenofovir, which significantly lowered infection rates. If transmission does occur, any treatment program would probably need to be focused on eradicating the virus during the 5- to 10-day window of the eclipse phase—before establishment of latency.

The Challenges of Developing HIV Vaccines

In the millions of HIV infections worldwide, there has not been a single known case in which the immune system has eradicated the virus. And although drugs have extended the lives of millions, they have had little effect on the pandemic overall. Overcoming AIDS may require a vaccine, something that so far has eluded researchers.

Obstacles to developing a vaccine for HIV have proved formidable, and there have been many unsuccessful vaccine trials over the decades. One challenge is that there is no model of natural immunity to mimic, and the use of attenuated viruses is too dangerous an option. Additionally, lack of an inexpensive small research animal hampers research. It is likely that a fundamentally different approach to vaccine development will be necessary.

Researchers also have concluded we likely need to know more about the basic mechanisms by which the body recognizes retroviruses before a successful vaccine can be developed. Retroviruses quickly integrate themselves into the DNA of the host cell, remaining latent and practically invisible to the immune system. These viruses also have a high mutation rate, even during the course of an infection, so numerous mutational variants of the virus arise. The virus has developed clades that differ substantially from one geographic area to another, and each would probably require an appropriate vaccine.

An experimental vaccine that is aimed at a target other than antibodies is undergoing development. The aim would be to make T cells similar to those found in elite controllers—people who manage to fend off infection when exposed to HIV.

Ideally, a vaccine would produce antibodies that prevent infection. In natural HIV infections, neutralizing antibodies develop rather slowly, appearing 2 months or so after transmission. By the time the immune system produces effective numbers of these

antibodies, the target envelope protein of the HIV has mutated and eludes neutralization. A successful vaccine would have to induce immunity before reservoirs of latent virus are established (see Figure 19.15), which may occur within 5 to 10 days of infection. In fact, a potential target for vaccination might be to prevent or regulate latency. It would also have to stimulate production of CTLs that are more effective than those usually produced in response to a natural infection. Finally, a vaccine would have to be affordable in regions of the world where economic subsistence is often marginal. All these factors make the development of an HIV vaccine an extremely difficult task.

The AIDS Epidemic and the Importance of Scientific Research

The AIDS epidemic gives clear evidence of the value of basic scientific research. Without the advances in molecular biology of the past century, we would have been unable even to identify the causative agent of AIDS. We would not have been able to develop the tests for screening donated blood, to identify points in the viral life cycle for which selectively toxic drugs could be developed, or even to monitor the course of the infection. In the lifetime of most of us, we will have the opportunity to witness medical history being made as the struggle with this deadly and elusive virus continues.

CHECK YOUR UNDERSTANDING

Does circumcision make a man more or less likely to acquire HIV infection? **19-31**

Clinical Case Resolved

Once the autoimmune rejection condition is recognized, Malik is successfully treated with Mab-CD3. Mab-CD3 binds the T cell receptor–CD3 complex on the surface of circulating T cells. This prevents the T cells from attacking host cells. Malik also receives cyclosporine, which suppresses IL-2 secretions—an essential chemical messenger in discrimination between self and nonself. If Malik had been diagnosed with DiGeorge syndrome before his transfusion, the blood could have been irradiated to destroy the white blood cells. Malik recovers from the GVHD, but he will eventually need a thymus transplant.

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Introduction (p. 515)

1. Hay fever, transplant rejection, and autoimmunity are examples of harmful immune reactions.
2. Immunosuppression is inhibition of the immune system.
3. Superantigens activate many T cell receptors that can cause adverse host responses.

Hypersensitivity (pp. 516–526)

1. Hypersensitivity reactions represent immunological responses to an antigen (allergen) that lead to tissue damage rather than immunity.
2. Hypersensitivity reactions occur when a person has been sensitized to an antigen.
3. Hypersensitivity reactions can be divided into four classes: types I, II, and III are immediate reactions based on humoral immunity, and type IV is a delayed reaction based on cell-mediated immunity.

Allergies and the Microbiome (p. 516)

4. Childhood exposure to microbes may decrease development of allergies.

Type I (Anaphylactic) Reactions (pp. 516–522)

5. Anaphylactic reactions involve the production of IgE antibodies that bind to mast cells and basophils to sensitize the host.
6. The binding of two adjacent IgE antibodies to an antigen causes the target cell to release chemical mediators, such as histamine, leukotrienes, and prostaglandins, which cause the observed allergic reactions.
7. Systemic anaphylaxis may develop in minutes after injection or ingestion of the antigen; this may result in circulatory collapse and death.
8. Localized anaphylaxis is exemplified by hives, hay fever, and asthma.
9. Skin testing is useful in determining sensitivity to an antigen.
10. Desensitization to an antigen can be achieved by repeated injections of the antigen, which leads to the formation of blocking (IgG) antibodies.

Type II (Cytotoxic) Reactions (pp. 522–524)

11. Type II reactions are mediated by IgG or IgM antibodies and complement.
12. The antibodies are directed toward foreign cells or host cells. Complement fixation may result in cell lysis. Macrophages and other cells may also damage the antibody-coated cells.
13. Human blood may be grouped into four principal types, designated A, B, AB, and O.
14. The presence or absence of two carbohydrate antigens designated A and B on the surface of the red blood cell determines a person's blood type.

15. Naturally occurring antibodies against the opposite AB antigen are present in serum.
16. Incompatible blood transfusions lead to the complement-mediated lysis of the donor red blood cells.
17. The absence of the Rh antigen in certain individuals (Rh^-) can lead to sensitization upon exposure to it.
18. An Rh^+ person can receive Rh^+ or Rh^- blood transfusions.
19. When an Rh^- person receives Rh^+ blood, that person will produce anti-Rh antibodies. Subsequent exposure to Rh^+ cells will result in a rapid, serious hemolytic reaction.
20. An Rh^- mother carrying an Rh^+ fetus will produce anti-Rh antibodies. Subsequent pregnancies involving Rh incompatibility may result in hemolytic disease of the newborn.
21. HDNB may be prevented by passive immunization of the mother with anti-Rh antibodies.
22. In the disease thrombocytopenic purpura, platelets are destroyed by antibodies and complement.
23. Agranulocytosis and hemolytic anemia result from antibodies against one's own blood cells coated with drug molecules.

Type III (Immune Complex) Reactions (pp. 524–525)

24. Immune complex diseases occur when IgG antibodies and soluble antigen form small complexes that lodge in the basement membranes of cells.
25. Subsequent complement fixation results in inflammation.
26. Glomerulonephritis is an immune complex disease.

Type IV (Delayed Cell-Mediated) Reactions (pp. 525–526)

27. Delayed cell-mediated hypersensitivity reactions are due primarily to T cell proliferation.
28. Sensitized T cells secrete cytokines in response to the appropriate antigen.
29. Cytokines attract and activate macrophages and initiate tissue damage.
30. The tuberculin skin test and allergic contact dermatitis are examples of delayed hypersensitivities.

Autoimmune Diseases (pp. 526–528)

1. Autoimmunity results from a loss of self-tolerance.
2. Self-tolerance occurs during fetal development; T cells that will target host cells are eliminated (clonal deletion) or inactivated.
3. Autoimmunity may be due to antibodies against infectious agents.
4. Graves' disease and myasthenia gravis are cytotoxic autoimmune reactions in which antibodies react to cell-surface antigens.
5. Systemic lupus erythematosus and rheumatoid arthritis are immune complex autoimmune reactions in which the deposition of immune complexes results in tissue damage.
6. Multiple sclerosis, insulin-dependent diabetes mellitus, and psoriasis are cell-mediated autoimmune reactions mediated by T cells.

Reactions Related to the Human Leukocyte Antigen (HLA) Complex (pp. 528–532)

1. MHC self molecules located on cell surfaces express genetic differences among individuals; these antigens are called HLAs in humans.
2. To prevent the rejection of transplants, HLA and ABO blood group antigens of the donor and recipient are matched as closely as possible.
3. Transplants recognized as foreign antigens may be lysed by T cells and attacked by macrophages and complement-fixing antibodies.
4. Transplantation to a privileged site (such as the cornea) or of a privileged tissue (such as pig heart valves) does not cause an immune response.
5. Pluripotent stem cells differentiate into a variety of tissues that may provide tissues for transplant.
6. Four types of transplants have been defined on the basis of genetic relationships between the donor and the recipient: autografts, isografts, allografts, and xenotransplants.
7. Bone marrow transplants (with immunocompetent cells) can cause graft-versus-host disease.
8. Successful transplant surgery often requires immunosuppressant drugs to prevent an immune response to the transplanted tissue.

The Immune System and Cancer (pp. 532–533)

1. Cancer cells are normal cells that have undergone transformation, divide uncontrollably, and possess tumor-associated antigens.
2. The response of the immune system to cancer is called immunological surveillance.
3. T_C cells recognize and lyse cancerous cells.
4. Cancer cells can escape detection and destruction by the immune system.
5. Cancer cells may grow faster than the immune system can respond.

Immunotherapy for Cancer (pp. 532–533)

6. Vaccines against liver and cervical cancer are available; a therapeutic vaccine against prostate cancer also has been approved.
7. Herceptin consists of monoclonal antibodies against a breast cancer growth factor.
8. Immunotoxins are chemical poisons linked to a monoclonal antibody; the antibody selectively locates the cancer cell for release of the poison.

Immunodeficiencies (pp. 533–534)

1. Immunodeficiencies can be congenital or acquired.
2. Congenital immunodeficiencies are due to defective or absent genes.
3. A variety of drugs, cancers, and infectious diseases can cause acquired immunodeficiencies.

Acquired Immunodeficiency Syndrome (AIDS) (pp. 534–544)

The Origin of AIDS (p. 535)

1. HIV is thought to have originated in Africa and was brought to other countries by modern transportation and unsafe sexual practices.

HIV Infection (pp. 535–540)

2. AIDS is the final stage of HIV infection.
3. HIV is a retrovirus with single-stranded RNA, reverse transcriptase, and a phospholipid envelope with gp120 spikes.

4. HIV spikes attach to $CD4^+$ and coreceptors on host cells; the $CD4^+$ receptor is found on T helper cells, macrophages, and dendritic cells.
5. Viral RNA is transcribed to DNA by reverse transcriptase. The viral DNA becomes integrated into the host chromosome to direct synthesis of new viruses or to remain latent as a provirus.
6. HIV evades the immune system in latency, in vacuoles, by using cell–cell fusion, and by antigenic change.
7. HIV-1 accounts for most HIV infections. Subtype B of HIV-1 is the most common type in the United States.
8. HIV infection is categorized by symptoms: phase 1 (asymptomatic), phase 2 (indicator opportunistic infections), and phase 3 ($CD4^+$ cells < 200 cells/μl).
9. The progression from HIV infection to AIDS takes about 10 years.
10. The life of an AIDS patient can be prolonged by the proper treatment of opportunistic infections.
11. People lacking CCR5 are resistant to HIV infection.
12. Elite controllers are long-term survivors who may hold the key to HIV treatment.

Diagnostic Methods (pp. 540–541)

13. HIV antibodies are detected by ELISA and Western blotting.
14. Plasma viral load tests detect viral nucleic acid and are used to quantify HIV in blood.

HIV Transmission (p. 541)

15. HIV is transmitted by sexual contact, breast milk, contaminated needles, transplacental infection, artificial insemination, and blood transfusion.
16. In developed countries, blood transfusions are not a likely source of infection because blood is tested for HIV antibodies.

AIDS Worldwide (p. 541)

17. Heterosexual intercourse is the primary method of HIV transmission.

Preventing and Treating AIDS (pp. 542–544)

18. Discouraging sexual promiscuity and using condoms and sterile needles prevent the transmission of HIV.
19. Vaccine development is difficult because the virus remains inside host cells and there is no model of natural immunity to mimic.
20. Current chemotherapeutic agents target the virus enzymes, including reverse transcriptase, integrase, and protease. Other inhibitors include cell entry inhibitors, maturation inhibitors, and tetherins.

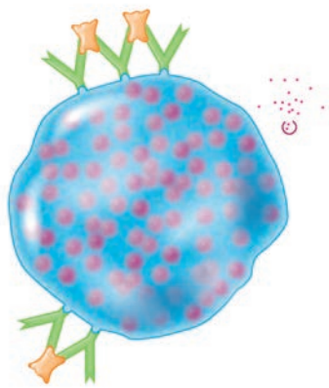
Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. DRAW IT Label IgE, antigen, and mast cell, and add an antihistamine to the following figure. What type of cell is this? Singulair stops inflammation by blocking leukotriene receptors. Add this action to the figure.



2. In the laboratory, blood is typed by looking for hemagglutination. For example, anti-A antibodies and type A RBCs clump. In a type A person, anti-A antibodies will cause hemolysis. Why?
3. Discuss the roles of antibodies and antigens in an incompatible tissue transplant.
4. Explain what happens when a person develops a contact sensitivity to poison oak.
   a. What causes the observed symptoms?
   b. How did the sensitivity develop?
   c. How might this person be desensitized to poison oak?
5. Why does an ANA (antinuclear antibody) test diagnose lupus?
6. Differentiate the three types of autoimmune diseases. Name an example of each type.
7. Summarize the causes of immunodeficiencies. What is the effect of an immunodeficiency?
8. In what ways do tumor cells differ antigenically from normal cells? Explain how tumor cells may be destroyed by the immune system.
9. If tumor cells can be destroyed by the immune system, how does cancer develop? What does immunotherapy involve?
10. NAME IT The Fc region of this protein causes degranulation when it binds to basophils.

Multiple Choice

1. Desensitization to prevent an allergic response can be accomplished by injecting small, repeated doses of
   a. IgE antibodies.
   b. the antigen (allergen).
   c. histamine.
   d. IgG antibodies.
   e. antihistamine.
2. What does *pluripotent* mean?
   a. Ability of a single cell to develop into an embryonic or adult stem cell.
   b. Ability of a stem cell to develop into many different cell types.
   c. A cell without MHC I and MHC II antigens.

d. Ability of a single stem cell to heal different types of diseases.
e. Ability of an adult cell to become a stem cell.

3. Cytotoxic autoimmunity differs from immune complex autoimmunity in that cytotoxic reactions
a. involve antibodies.
b. do not involve complement.
c. are caused by T cells.
d. do not involve IgE antibodies.
e. none of the above

4. Antibodies against HIV are ineffective for all of the following reasons *except*
a. the fact that antibodies aren't made against HIV.
b. transmission by cell–cell fusion.
c. antigenic changes.
d. latency.
e. persistence of virus particles in vacuoles.

5. Which of the following is *not* the cause of a natural immunodeficiency?
a. a recessive gene resulting in lack of a thymus gland
b. a recessive gene resulting in few B cells
c. HIV infection
d. immunosuppressant drugs
e. All of the above are causes of natural immunodeficiency.

6. Which antibodies will be found naturally in the serum of a person with blood type A, Rh^+?
a. anti A, anti B, anti Rh
b. anti A, anti Rh
c. anti A
d. anti B, anti Rh
e. anti B

Use the following choices to match the type of hypersensitivity to the examples in questions 7 through 10.
a. type I hypersensitivity
b. type II hypersensitivity
c. type III hypersensitivity
d. type IV hypersensitivity
e. all of the above

7. Localized anaphylaxis.
8. Allergic contact dermatitis.
9. Due to immune complexes.
10. Reaction to an incompatible blood transfusion.

Analysis

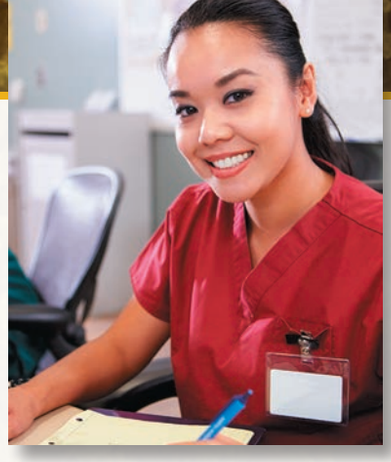
1. When and how does our immune system discriminate between self and nonself antigens?
2. The first preparations used for artificially acquired passive immunity were antibodies in horse serum. A complication that resulted from the therapeutic use of horse serum was immune complex disease. Why did this occur?
3. Do people with AIDS make antibodies? If so, why are they said to have an immunodeficiency?
4. What are the methods of action of anti-AIDS drugs?

Clinical Applications and Evaluation

1. Fungal infections such as athlete's foot are chronic. These fungi degrade skin keratin but are not invasive and do not produce toxins. Why do you suppose that many of the symptoms of a fungal infection are due to hypersensitivity to the fungus?
2. After working in a mushroom farm for several months, a worker develops these symptoms: hives, edema, and swelling lymph nodes.
a. What do these symptoms indicate?
b. What mediators cause these symptoms?
c. How may sensitivity to a particular antigen be determined?
d. Other employees do not appear to have any immunological reactions. What could explain this?

(*Hint:* The allergen is conidiospores from molds growing in the mushroom farm.)

3. Physicians administering live, attenuated mumps and measles vaccines prepared in chick embryos are instructed to have epinephrine available. Epinephrine will not treat these viral infections. What is the purpose of keeping this drug on hand?
4. A woman with blood type A+ once received a transfusion of AB+ blood. When she carried a type B+ fetus, the fetus developed hemolytic disease of the newborn. Explain why this fetus developed this condition even though another type B+ fetus in a different type A+ mother was normal.



In the Clinic

Your family knows you are a nurse and always asks you for advice. Your brother asks you about his cough, which started two weeks ago. Now he's coughing up mucus and feels sure that it's bronchitis. He asks you whether he should use the amoxicillin he saved from a prescription he received when he had bronchitis last winter. **What should you tell your brother?**

Hint: Read about preventing microbial resistance on page 572.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

20

Antimicrobial Drugs

When the body's normal defenses cannot prevent or overcome a disease, it often can be treated by chemotherapy with antimicrobial drugs. Like the disinfectants discussed in Chapter 7, antimicrobial drugs act by killing or by interfering with the growth of microorganisms. Unlike disinfectants, however, antimicrobial drugs must often act *within* the host without damaging the host. This is the important principle of selective toxicity.

Antibiotics were one of the most important discoveries of modern medicine. Many people remember a time when little could be done to treat many lethal infectious diseases. The introduction of penicillin, sulfanilamide, and other antimicrobials to treat conditions such as a ruptured appendix or so-called blood poisoning (sepsis) resulted in cures that seemed almost miraculous.

Today, we are seeing the advances represented by these miracle drugs threatened by the development of antibiotic resistance. For example, there are frequent reports of staphylococcal pathogens that are resistant to practically all the available antibiotics. Certain populations of the pathogens causing tuberculosis are now resistant to essentially all of the available antibiotics that were once effective. The Clinical Case in this chapter describes an infection caused by the antibiotic-resistant *Pseudomonas aeruginosa* shown in the photograph. In some cases, medicine now has only a few more weapons to treat the diseases caused by these pathogens than were available a century ago.

***Pseudomonas aeruginosa* (blue) are resistant to many antibiotics.**

The History of Chemotherapy

LEARNING OBJECTIVES

20-1 Identify the contributions of Paul Ehrlich and Alexander Fleming to chemotherapy.

20-2 Name the microbes that produce most antibiotics.

The birth of modern chemotherapy is credited to the efforts of Paul Ehrlich in Germany during the early part of the twentieth century. While attempting to stain bacteria without staining the surrounding tissue, he speculated about some "magic bullet" that would selectively find and destroy pathogens but not harm the host. This idea provided the basis for both **selective toxicity** and **chemotherapy,** a term he coined.

In 1928, Alexander Fleming observed that the growth of the bacterium *Staphylococcus aureus* was inhibited in the area surrounding the colony of a mold that had contaminated a Petri plate (Figure 1.5, page 11). The mold was identified as *Penicillium notatum,* and its active compound, which was isolated a short time later, was named penicillin. Similar inhibitory reactions between colonies on solid media are commonly observed in microbiology, and the mechanism of inhibition is called *antibiosis* (Figure 20.1). From this word comes the term **antibiotic,** a substance produced by microorganisms that in small amounts inhibits another microorganism. Therefore, the wholly synthetic sulfa drugs, for example, are technically **antimicrobial drugs,** not antibiotics, a distinction often ignored in practice. The discovery of sulfa drugs arose from a systematic survey of chemicals by German industrial scientists beginning in 1927. In 1932, a compound termed Prontosil Red, a sulfanilamide-containing dye, was found to control streptococcal infections in mice. During World War II, the Allied armies made wide use of this sulfanilamide compound. The discovery and use of sulfa drugs made it clear that practical antimicrobials could be effective against systemic bacterial infections and resurrected interest in the earlier reports of penicillin.

In 1940 the first clinical trials of penicillin took place. Under wartime conditions in the United Kingdom, research into the development and large-scale production of penicillin was not possible, and this work was transferred to the United States. The original culture of *P. notatum* was not a very efficient producer of the antibiotic. It was soon replaced by a more prolific strain. This valuable organism (a strain of *Penicillium chrysogenum*) was first isolated from a moldy cantaloupe bought at a market in Peoria, Illinois.

Antibiotic Use and Discovery Today

Antibiotics are actually rather easy to discover, but few are of medical or commercial value. Some are used commercially rather than for treating disease—for example, as a supplement in animal feed (see the Clinical Focus box on page 573). There is an increasing urgency to find an answer to the growing problem of **antibiotic resistance,** a phenomenon in which formerly effective medications have less and less impact on bacteria.



Figure 20.1 Laboratory observation of antibiosis. Anyone plating out microbes from natural environments, especially soil, will frequently see examples of bacterial inhibition by antibiotics produced by bacteria, most commonly *Streptomyces* species.

Q Would there be any advantage to a soil microbe to produce an antibiotic?

More than half of our antibiotics are produced by species of *Streptomyces,* filamentous bacteria that commonly inhabit soil. A few antibiotics are produced by endospore-forming

Clinical Case: Sight Unseen

Ophthalmic surgeon Dr. Vanessa Singh has performed hundreds of corneal transplants without incident. She is understandably worried when a 76-year-old woman on whom she operated yesterday develops a corneal infection. Dr. Singh had given her patient the proper prophylactic subconjunctival injection of gentamicin following transplantation, so she is puzzled by the presence of infection. Postoperative gentamicin is recommended for corneal transplants because *Staphylococcus epidermidis* and *S. aureus* are the most common organisms causing postoperative eye infection.

Dr. Singh takes a culture from the patient's eye and sends it to the lab for analysis. The culture comes back positive for *Pseudomonas aeruginosa*. Dr. Singh checks with the eye bank and discovers that a 30-year-old man who received the other cornea from the donor developed a *P. aeruginosa* infection within 24 hours of surgery. This patient also had received prophylactic gentamicin to prevent infection.

What does Dr. Singh need to know? Read on to find out.

549 560 569 571 574 575

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
GRAM-POSITIVE RODS	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
ACTINOMYCETES	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Saccharopolyspora erythraea	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpurea	Gentamicin
FUNGI	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium chrysogenum	Penicillin

bacteria such as *Bacillus,* and others are produced by molds, mostly of the genera *Penicillium* and *Cephalosporium* (SEF-ah-lō-spor′ē-um). See Table 20.1 for the sources of many antibiotics in use today—a surprisingly limited group of organisms. One study screened 400,000 microbial cultures that yielded only three useful drugs. It's especially interesting to note that practically all antibiotic-producing microbes have some sort of sporulation process.

Most antibiotics in use today were discovered by methods that required identifying and growing colonies of antibiotic-producing organisms, mostly by screening soil samples. It's rather easy to identify microbes in such samples that have antimicrobial activity; however, many are toxic or not commercially useful. Also, these proved to be examples of "low-hanging fruit," and continued work often resulted in discovery of the same antibiotics. For example, about 1 in every 100 actinomycetes in soil produce streptomycin, and 1 in 250 produce tetracycline. To find an antibiotic that is produced by only one soil or sea microbe in 10 million is a daunting task. Even modern *high-throughput methods,* which rapidly screen very large numbers of microbes in the search for new antibiotics, have failed to yield many new discoveries. In fact, in the past 40 years, research using established methods has led to the clinical use of only a couple of new structural types of microbial inhibitors.

CHECK YOUR UNDERSTANDING

- Who coined the term *chemotherapy*? **20-1**
- More than half our antibiotics are produced by a certain genus of bacteria. What is it? **20-2**

Spectrum of Antimicrobial Activity

LEARNING OBJECTIVES

20-3 Describe the problems of chemotherapy for viral, fungal, protozoan, and helminthic infections.

20-4 Define the following terms: *spectrum of activity, broad-spectrum antibiotic, superinfection.*

It's comparatively easy to find or develop drugs that are effective against prokaryotic cells and that do not affect the eukaryotic cells of humans. These two cell types differ substantially in many ways, such as in the presence or absence of cell walls, the fine structure of their ribosomes, and details of their metabolism. Thus, selective toxicity has numerous targets. The problem is more difficult when the pathogen is a eukaryotic cell, such as a fungus, protozoan, or helminth. At the cellular level, these organisms resemble the human cell much more closely than a bacterial cell does. So, a drug that targets these pathogens usually damages the host, too. Our arsenal against these types of pathogens is much more limited than our arsenal of antibacterial drugs. Viral infections are also particularly difficult to treat because the pathogen is within the human host's cells and because the genetic information of the virus is directing the human cell to make viruses rather than to synthesize normal cellular materials.

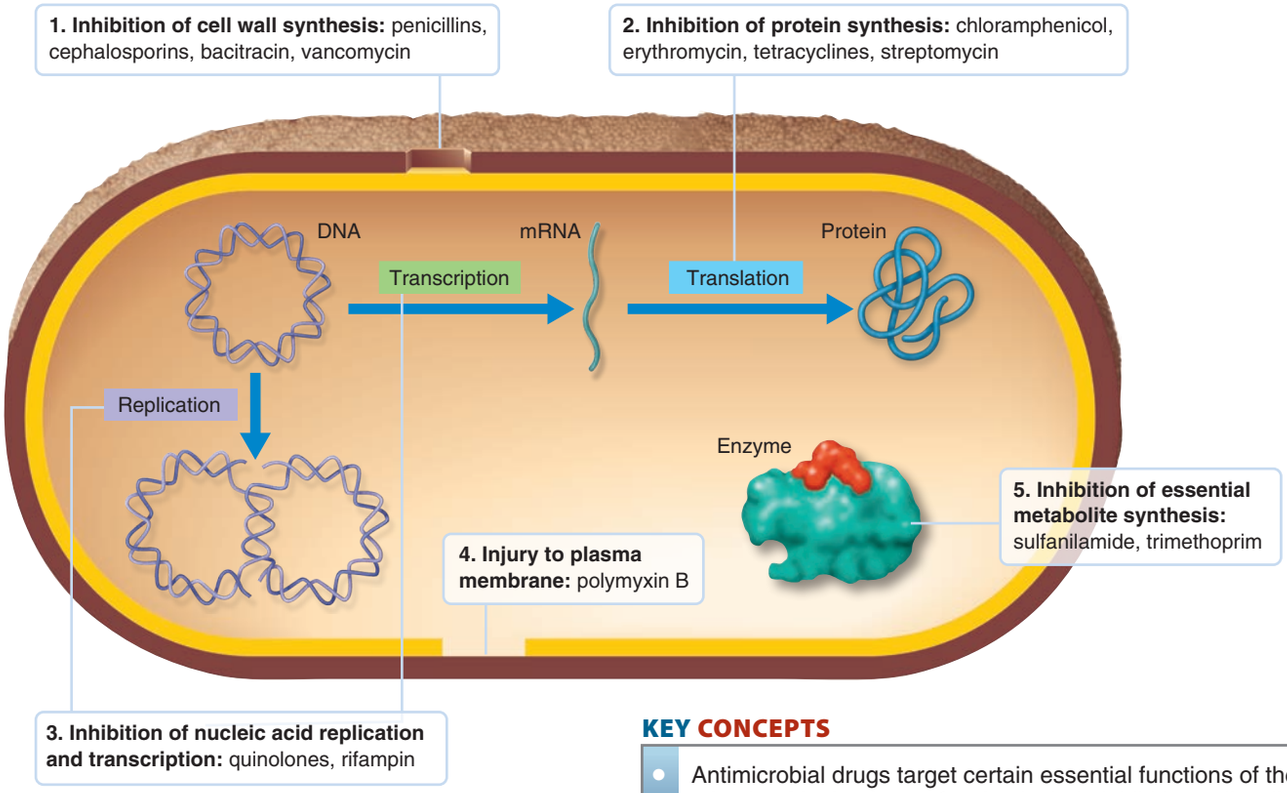
Some drugs have a **narrow spectrum of microbial activity,** or range of different microbial types they affect. Penicillin G, for example, affects gram-positive bacteria but very few gram-negative bacteria. Antibiotics that affect a broad range of gram-positive or gram-negative bacteria are therefore called **broad-spectrum antibiotics.**

A primary factor involved in the selective toxicity of antibacterial action lies in the lipopolysaccharide outer layer of gram-negative bacteria and the porins that form water-filled channels across this layer (see Figure 4.13c, page 82). Drugs that pass through the porin channels must be relatively small and preferably hydrophilic. Drugs that are lipophilic (having an affinity for lipids) or especially large do not enter gram-negative bacteria readily.

Table 20.2 summarizes the spectrum of activity of a number of chemotherapeutic drugs. Because the identity of the pathogen is not always immediately known, a broad-spectrum drug would seem to have an advantage in treating a disease by saving valuable time. The disadvantage is that these drugs destroy many normal microbiota of the host. The normal microbiota ordinarily compete with and check the growth of pathogens or other microbes. If the antibiotic does not destroy certain organisms in the normal microbiota but does destroy their competitors, the survivors may flourish and become opportunistic pathogens. An example that sometimes occurs is overgrowth by the yeastlike fungus *Candida albicans,* which is not sensitive to bacterial antibiotics. This overgrowth is called a **superinfection,** a

FOUNDATION FIGURE 20.2

Major Action Modes of Antibacterial Drugs



KEY CONCEPTS

- Antimicrobial drugs target certain essential functions of the microbe. Mechanisms of action include inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.
- The antimicrobial drug must not interfere with essential functions of the microbe's host.

term that is also applied to growth of a target pathogen that has developed resistance to the antibiotic. In this situation, such an antibiotic-resistant strain replaces the original sensitive strain, and the infection continues.

CHECK YOUR UNDERSTANDING

- Identify at least one reason why it's so difficult to target a pathogenic virus without damaging the host's cells. **20-3**
- Why are antibiotics with a very broad spectrum of activity not as useful as one might first think? **20-4**

The Action of Antimicrobial Drugs

LEARNING OBJECTIVE

20-5 Identify five modes of action of antimicrobial drugs.

Antimicrobial drugs are either **bactericidal** (they kill microbes directly) or **bacteriostatic** (they prevent microbes from growing). In bacteriostasis, the host's own defenses, such as phagocytosis and antibody production, usually destroy the microorganisms. The major modes of action are summarized in Figure 20.2.

Inhibiting Cell Wall Synthesis

Penicillin, the first true antibiotic to be discovered and used if one does not also consider the sulfa drugs, is an example of an inhibitor of cell wall synthesis.

The cell wall of a bacterium consists of a macromolecular network called peptidoglycan. Recall from Chapter 4 that peptidoglycan is found only in bacterial cell walls. Penicillin and certain other antibiotics prevent the synthesis of intact peptidoglycan; consequently, the cell wall is greatly weakened,

TABLE 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
Isoniazid ⟷		Penicillin G ⟷		Ketoconazole ⟷		Niclosamide (tapeworms) ⟷	
Streptomycin ⟷					Mefloquine (malaria) ⟷		Acyclovir ⟷
Tetracycline ⟷						Praziquantel (flukes) ⟷	

*Growth of these bacteria frequently occurs within macrophages or tissue structures.
†Obligately intracellular bacteria.

and the cell undergoes lysis (Figure 20.3). Because penicillin targets the synthesis process, only actively growing cells are affected by these antibiotics—and, because human cells do not have peptidoglycan cell walls, penicillin has very little toxicity for host cells.

Inhibiting Protein Synthesis

Because protein synthesis is a common feature of all cells, whether prokaryotic or eukaryotic, it would seem an unlikely target for selective toxicity. One notable difference between prokaryotes and eukaryotes, however, is the structure of their ribosomes. Eukaryotic cells have 80S ribosomes whereas prokaryotic cells have 70S ribosomes (Chapter 4, page 91). The difference in ribosomal structure accounts for the selective toxicity of antibiotics that affect protein synthesis. However, mitochondria (important eukaryotic organelles) also contain 70S ribosomes similar to those of bacteria. Antibiotics targeting the 70S ribosomes can therefore have adverse effects on the cells of the host. Among the antibiotics that interfere with protein synthesis are chloramphenicol, erythromycin, streptomycin, and the tetracyclines (Figure 20.4).

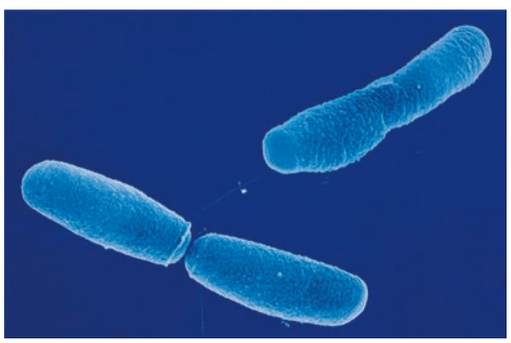
Injuring the Plasma Membrane

Certain antibiotics, especially polypeptide antibiotics, bring about changes in the permeability of the plasma membrane that result in the loss of important metabolites from the microbial cell.

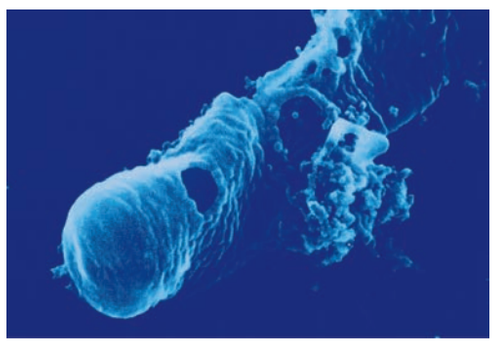
Some antifungal drugs, such as amphotericin B, miconazole, and ketoconazole, are effective against a considerable range of fungal diseases. Such drugs combine with sterols in the fungal plasma membrane to disrupt the membrane (Figure 20.5). Because bacterial plasma membranes generally lack sterols, these antibiotics do not act on bacteria.

Inhibiting Nucleic Acid Synthesis

A number of antibiotics interfere with the processes of DNA replication and transcription in microorganisms. Some drugs with this mode of action have an extremely limited usefulness because they interfere with mammalian DNA and RNA as well.



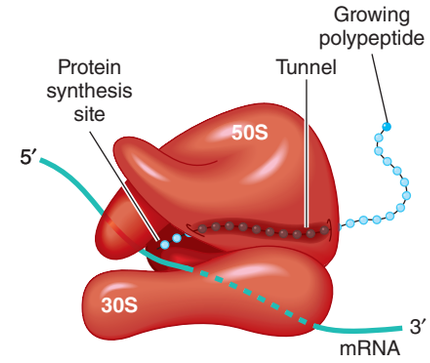
(a) Rod-shaped bacterium before penicillin



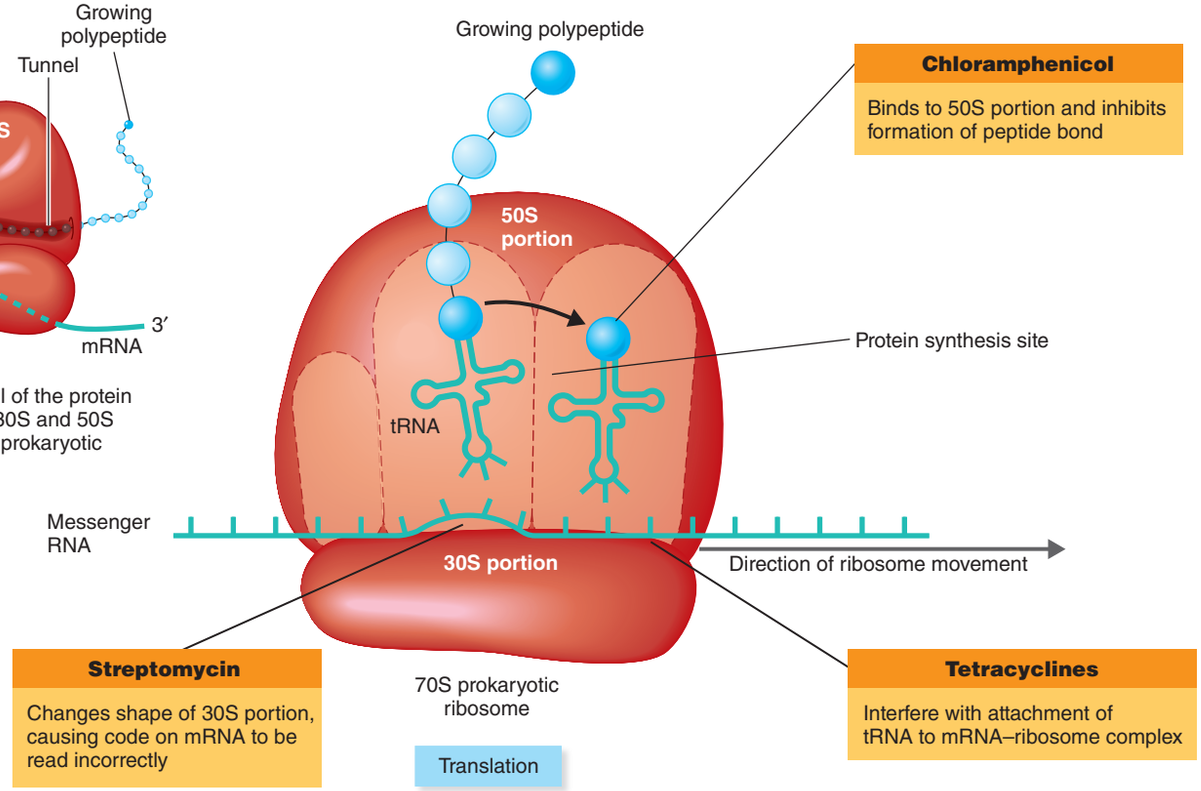
(b) The bacterial cell lysing as penicillin weakens the cell wall

Figure 20.3 The inhibition of bacterial cell wall synthesis by penicillin.

Q Why don't penicillins affect the human cell?



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome



(b) Diagram indicating the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities

Figure 20.4 The inhibition of protein synthesis by antibiotics. **(a)** The inset shows how the 70S prokaryotic ribosome is assembled from two subunits, 30S and 50S. Note how the growing peptide chain passes through a tunnel in the 50S subunit from the site of protein synthesis. **(b)** The diagram shows the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities.

Q Why do antibiotics that inhibit protein synthesis affect bacteria and not human cells?

Inhibiting the Synthesis of Essential Metabolites

A particular enzymatic activity of a microorganism can be *competitively inhibited* by a substance (*antimetabolite*) that closely resembles the normal substrate for the enzyme (see Figure 5.7, page 116). An example of competitive inhibition is the relationship between the antimetabolite sulfanilamide (a sulfa drug) and ***para*-aminobenzoic acid (PABA).** In many microorganisms, PABA is the substrate for an enzymatic reaction leading to the synthesis of folic acid, a vitamin that functions as a coenzyme for the synthesis of the purine and pyrimidine bases of nucleic acids and many amino acids. MM **Animation** Chemotherapeutic Agents: Modes of Action

CHECK YOUR UNDERSTANDING

What cellular function is inhibited by tetracyclines? **20-5**

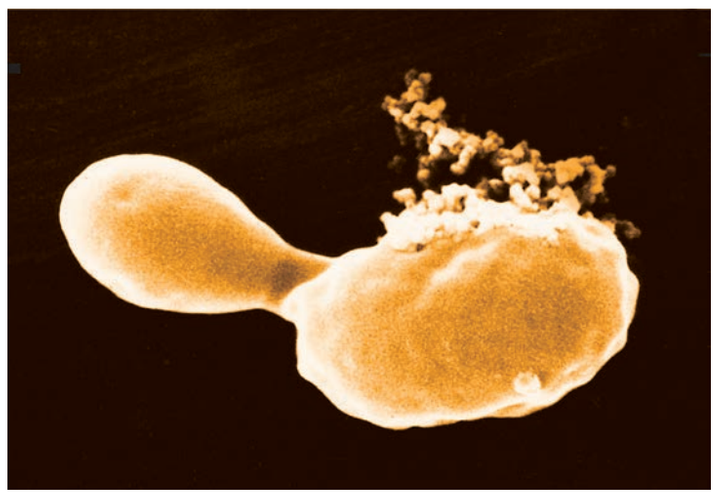


Figure 20.5 Injury to the plasma membrane of a yeast cell caused by an antifungal drug. The cell releases its cytoplasmic contents as the plasma membrane is disrupted by the antifungal drug miconazole.

Q Many antifungal drugs combine with sterols in the plasma membrane. don't they combine with sterols in human cell membranes?

Common Antimicrobial Drugs

LEARNING OBJECTIVES

20-6 Explain why drugs in this section are bacteria-specific.

20-7 List the advantages of each of the following over penicillin: semisynthetic penicillins, cephalosporins, and vancomycin.

20-8 Explain why isoniazid and ethambutol are antimycobacterial agents.

20-9 Describe how each of the following inhibits protein synthesis: aminoglycosides, tetracyclines, chloramphenicol, macrolides.

20-10 Compare polymyxin B, bacitracin, and neomycin in their modes of action.

20-11 Describe how rifamycins and quinolones kill bacteria.

20-12 Describe how sulfa drugs inhibit microbial growth.

20-13 Explain modes of action of current antifungal drugs.

20-14 Explain modes of action of current antiviral drugs.

20-15 Explain modes of action of current antiprotozoan and antihelminthic drugs.

Table 20.3 summarizes the commonly used antibacterial drugs. Table 20.4 summarizes the cephalosporins, one group of antibacterial drugs. Table 20.5 summarizes the commonly used drugs effective against fungi, viruses, protozoans, and helminths.

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

For antibiotics to function as a "magic bullet," they usually must target microbial structures or functions that are not shared with mammalian structures or functions. The eukaryotic mammalian cell usually does not have a cell wall; instead, it has only a plasma membrane (see Chapter 4). Even this membrane differs in composition from the plasma membrane of prokaryotic cells. For this reason, the microbial cell wall is an attractive target for the action of antibiotics.

Penicillin

The term **penicillin** refers to a group of over 50 chemically related antibiotics (Figure 20.6). All penicillins have a common core structure containing a β-lactam ring called the nucleus. Types are differentiated by the chemical side chains attached to their nuclei. Penicillins prevent the cross-linking of the peptidoglycans, which interferes with the final stages of the construction of the cell walls, primarily of gram-positive bacteria (see Figure 4.13a, page 82). Penicillins can be produced either naturally or semisynthetically.

Natural Penicillins Penicillins extracted from cultures of the mold *Penicillium* are the so-called **natural penicillins** (Figure 20.6a). The prototype compound of all the penicillins is

TABLE 20.3 Antibacterial Drugs

Drugs by Mode of Action	Comments
INHIBITORS OF CELL WALL SYNTHESIS	
Natural Penicillins	
Penicillin G	Against gram-positive bacteria, requires injection
Penicillin V	Against gram-positive bacteria, oral administration
Semisynthetic Penicillins	
Oxacillin	Resistant to penicillinase
Ampicillin	Broad spectrum
Amoxicillin	Broad spectrum; combined with inhibitor of penicillinase
Aztreonam	A monobactam; effective against gram-negative bacteria, including *Pseudomonas* spp.
Imipenem	A carbapenem; very broad spectrum
Cephalosporins	
Cephalothin	First-generation cephalosporin; activity similar to penicillin; requires injection
Cefixime	Fourth-generation cephalosporin; oral administration
Polypeptide Antibiotics	
Bacitracin	Against gram-positive bacteria; topical application
Vancomycin	A glycopeptide type; penicillinase-resistant; against gram-positive bacteria
Antimycobacterial Antibiotics	
Isoniazid	Inhibits synthesis of mycolic acid component of cell wall of *Mycobacterium* spp.
Ethambutol	Inhibits incorporation of mycolic acid into cell wall of *Mycobacterium* spp.

TABLE 20.3 *(continued)*

Drugs by Mode of Action	Comments
INHIBITORS OF PROTEIN SYNTHESIS	
Chloramphenicol	Broad spectrum, potentially toxic
Aminoglycosides	
Streptomycin	Broad spectrum, including mycobacteria
Neomycin	Topical use, broad spectrum
Gentamicin	Broad spectrum, including *Pseudomonas* spp.
Pleuromutilins	
Mutilin, retpamulin	Inhibit gram-positive bacteria
Tetracyclines	
Tetracycline, oxytetracycline, chlortetracycline	Broad spectrum, including chlamydias and rickettsias; animal feed additives
Macrolides	
Erythromycin	Alternative to penicillin
Azithromycin, clarithromycin	Semisynthetic; broader spectrum and better tissue penetration than erythromycin
Telithromycin (Ketek)	New generation of semisynthetic macrolides; used to cope with resistance to other macrolides
Streptogramins	
Quinupristin and dalfopristin (Synercid)	Alternative for treating vancomycin-resistant gram-positive bacteria
Oxazolidinones	
Linezolid (Zyvox)	Useful primarily against penicillin-resistant gram-positive bacteria
Glycylcyclines	
Tygecycline	Broad spectrum, especially MRSA and *Acinetobacter*
INJURY TO THE PLASMA MEMBRANE	
Polymyxin B	Topical use, gram-negative bacteria, including *Pseudomonas* spp.
Lipopeptides	
Daptomycin	To treat MRSA infections
INHIBITORS OF NUCLEIC ACID SYNTHESIS	
Rifamycins	
Rifampin	Inhibits synthesis of mRNA; treatment of tuberculosis
Quinolones and Fluoroquinolones	
Nalidixic acid, nofloxacin, ciprofloxacin	Inhibit DNA synthesis; broad spectrum; urinary tract infections
Gatifloxacin	Newest generation quinolone; increased potency against gram-positive bacteria
COMPETITIVE INHIBITORS OF THE SYNTHESIS OF ESSENTIAL METABOLITES	
Sulfonamides	
Trimethoprim-sulfamethoxazole	Broad spectrum; combination is widely used

TABLE 20.4 Differential Grouping of Cephalosporins

Generation	Description	Example
First	Relatively narrow level of activity, primarily against gram-negative bacteria	Cephalothin
Second	More extended gram-negative spectrum	Cefamdole (IV) Cefaclor (oral)
Third	Most active against gram-negative bacteria, including some pseudomonads; must be injected	Ceftazidime
Fourth	Require injections; most extended spectrum of activity	Cefepime

TABLE 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs

	Mode of Action	Comments
ANTIFUNGAL DRUGS		
Agents Affecting Fungal Sterols (Plasma Membrane)		
Polyenes		
Amphotericin B	Injury to plasma membrane	Systemic fungal infections; fungicidal
Azoles		
Clotrimazole, miconazole	Inhibit synthesis of plasma membrane	Topical use
Ketoconazole	Inhibits synthesis of plasma membrane	Can be taken orally for systemic fungal infections
Allylamines		
Terbinafine, naftifine	Inhibit synthesis of plasma membrane	Treatment of diseases resistant to azoles
Agents Affecting Fungal Cell Walls		
Echinocandins		
Caspofungin (Cancidas)	Inhibits synthesis of cell wall	Intravenous use only
Agents Inhibiting Nucleic Acids		
Flucytosine	Inhibits RNA synthesis	Usually in combination with other antifungals
Other Antifungal Drugs		
Griseofulvin	Inhibition of mitotic microtubules	Fungal infections of the skin
Tolnaftate	Unknown	Athlete's foot
ANTIVIRAL DRUGS		
Entry and Fusion Inhibitors		
Maraviroc	Binds CCR5	Treatment of HIV
Zanamivir, oseltamivir	Inhibit neuraminidase on influenza virus	Treatment of influenza
Uncoating Inhibitors		
Amantadine, zimantadine	Inhibit uncoating	Treatment of influenza
Genome Integration and Nucleic Acid Synthesis Inhibitors		
Zidovudine (AZT)	Inhibits DNA or RNA synthesis	Used primarily against HIV
Acyclovir, ganciclovir, ribavirin, lamivudine	Inhibit DNA or RNA synthesis	Used primarily against herpesviruses
Cidofovir	Inhibits DNA or RNA synthesis	Cytomegalovirus infections; possibly effective against smallpox
Adefovir dipivoxil (Hepsera)	Competitive inhibitor for HBV reverse transcriptase	Treatment of lamivudine-resistant infections
Assembly and Exit Inhibitors		
Saquinavir	Protease inhibitor	Treatment of HIV
Boceprevir	Protease inhibitor	Treatment of hepatitis C
Zanamivir, oseltamivir	Neuraminidase inhibitor	Treatment of influenza
Interferons		
Alpha interferon	Inhibits spread of virus to new cells	Viral hepatitis
ANTIPROTOZOAN DRUGS		
Chloroquine	Inhibits DNA synthesis	Malaria; effective against red blood cell stage only
Diiodohydroxyquin	Unknown	Amebic infections; amebicidal
Metronidazole, tinidazole	Interfere with anaerobic metabolism	Giardiasis, amebiasis, trichomoniasis

TABLE 20.5 *(continued)*

	Mode of Action	Comments
ANTIHELMINTHIC DRUGS		
Niclosamide	Prevents ATP generation in mitochondria	Tapeworm infections; kills tapeworms
Praziquantel	Alters permeability of plasma membranes	Tapeworm and fluke infections; kills flatworms
Pyrantel pamoate	Neuromuscular block	Intestinal roundworms; kills roundworms
Mebendazole, albendazole	Inhibit absorption of nutrients	Intestinal roundworms
Ivermectin	Paralyzes worm	Intestinal roundworms primarily; occasional use for scabies mite and lice

penicillin G. It has a narrow but useful spectrum of activity and is often the drug of choice against most staphylococci, streptococci, and several spirochetes. When injected intramuscularly, penicillin G is rapidly excreted from the body in 3 to 6 hours (Figure 20.7). When taken orally, the acidity of the digestive fluids in the stomach diminishes its concentration. *Procaine penicillin,* a combination of the drugs procaine and penicillin G, is retained at detectable concentrations for up to 24 hours; the concentration peaks at about 4 hours. Still longer retention times can be achieved with *benzathine penicillin,* a combination of benzathine and penicillin G. Although retention times of as long as 4 months can be obtained, the concentration of the drug is so low that the organisms must be very sensitive to it. Penicillin V, which is stable in stomach acids and can be taken orally, and penicillin G are the natural penicillins most often used.

Natural penicillins have some disadvantages. Chief among them are their narrow spectrum of activity and their susceptibility to penicillinases. *Penicillinases* are enzymes produced by many bacteria, most notably *Staphylococcus* species, that cleave the β-lactam ring of the penicillin molecule (Figure 20.8). Because of this characteristic, penicillinases are sometimes called *β-lactamases.*

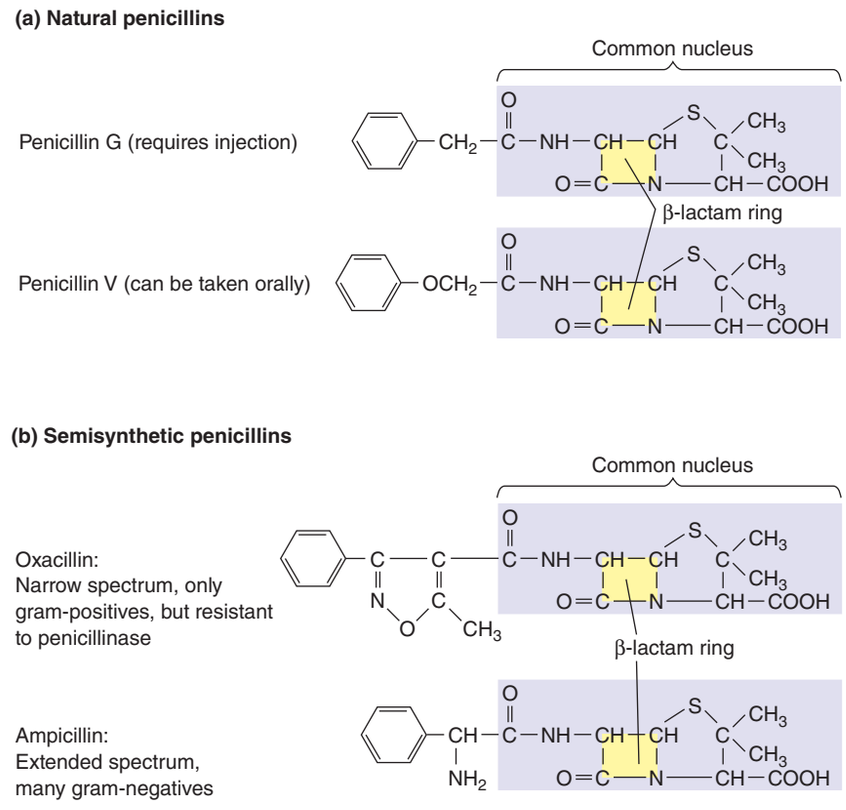


Figure 20.6 The structure of penicillins, antibacterial antibiotics. The portion that all penicillins have in common—which contains the (yellow) β-lactam ring—is shaded in purple. The unshaded portions represent the side chains that distinguish one penicillin from another.

Q What does *semisynthetic* mean?

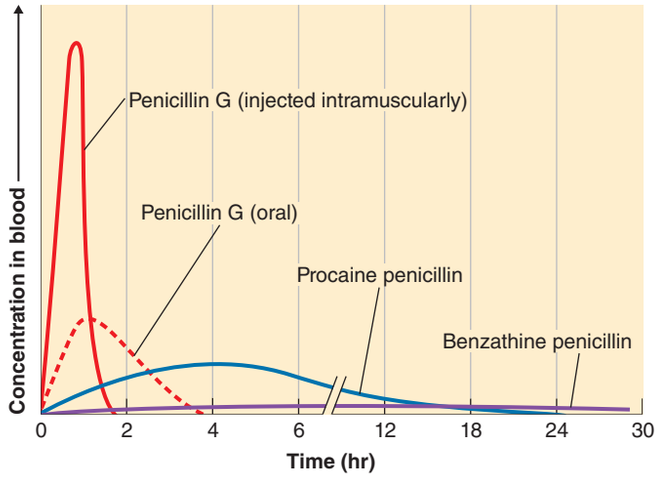


Figure 20.7 Retention of penicillin G. Penicillin G is normally injected (solid red line); when administered by this route, the drug is present in high concentrations in the blood but disappears quickly. Taken orally (dotted red line), penicillin G is destroyed by stomach acids and is not very effective. It's possible to improve retention of penicillin G by combining it with compounds such as procaine and benzathine (blue and purple lines). However, the blood concentration reached is low, and the target bacterium must be extremely sensitive to the antibiotic.

Q How does a low concentration of penicillin G select for penicillin-resistant bacteria?

Semisynthetic Penicillins A large number of **semisynthetic penicillins** have been developed in attempts to overcome the disadvantages of natural penicillins (Figure 20.6b). Scientists develop these penicillins in either of two ways. First, they can interrupt synthesis of the molecule by *Penicillium* and obtain only the common penicillin nucleus for use. Second, they can remove the side chains from the completed natural molecules and then chemically add other side chains that make them more resistant to penicillinase, or the scientists can give them an extended spectrum. Thus the term *semisynthetic:* part of the penicillin is produced by the mold, and part is added synthetically.

Penicillinase-Resistant Penicillins Resistance of staphylococcal infections to penicillin soon became a problem because of a plasmid-borne gene for β-lactamase. Antibiotics that were relatively resistant to this enzyme, such as the semisynthetic penicillin *methicillin,* were introduced, but resistance to them also soon appeared; thus the organisms were termed **methicillin-resistant *Staphylococcus aureus* (MRSA),** usually pronounced *mersa* (see the Clinical Focus box in Chapter 14, page 411). Resistance became so prevalent that methicillin has been discontinued in the United States. The term has come to be applied to strains that have developed resistance to a wide range of penicillins and cephalosporins. This includes other penicillinase-resistant antibiotics, such as *oxacillin,* and those combined with β-lactamase inhibitors. See the discussion of antibiotic resistance on page 569.

Extended-Spectrum Penicillins To overcome the problem of the narrow spectrum of activity of natural penicillins, broader-spectrum semisynthetic penicillins have been developed. These new penicillins are effective against many gram-negative bacteria as well as gram-positive ones, although they are not resistant to penicillinases.

The first such penicillins were the aminopenicillins, such as *ampicillin* and *amoxicillin.*

When bacterial resistance to these became more common, the carboxypenicillins were developed. Members of this group, such as *carbenicillin* and *ticarcillin,* have even greater activity against gram-negative bacteria and have the special advantage of activity against *Pseudomonas aeruginosa.*

Among the more recent additions to the penicillin family are the ureidopenicillins, such as *mezlocillin* and *azlocillin.* These broader-spectrum penicillins are modifications of the structure of ampicillin. The search for even more effective modifications of penicillin continues.

Penicillins Plus β-Lactamase Inhibitors A different approach to the proliferation of penicillinase is to combine penicillins with *potassium clavulanate (clavulanic acid),* a product of a streptomycete. Potassium clavulanate is a noncompetitive inhibitor of penicillinase with essentially no antimicrobial activity of its own. It has been combined with some new broader-spectrum penicillins, such as *amoxicillin.* The combination is best known by its trade name, Augmentin.

Carbapenems

The **carbapenems** are a class of β-lactam antibiotics that substitute a carbon atom for a sulfur atom and add a double bond

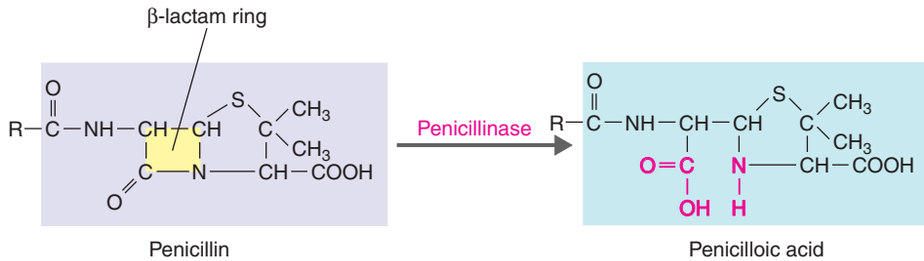


Figure 20.8 The effect of penicillinase on penicillins. Bacterial production of this enzyme, which is shown breaking the β–lactam ring, is by far the most common form of resistance to penicillins. R is an abbreviation for the chemical side groups that differentiate similar or otherwise-identical compounds.

Q What is penicillinase?

to the penicillin nucleus. These antibiotics inhibit cell wall synthesis and have an extremely broad spectrum of activity. Representative of this group is Primaxin, a combination of *imipenem* and *cilastatin.* The cilastatin has no antimicrobial activity but prevents degradation of the combination in the kidneys. Tests have demonstrated that Primaxin is active against 98% of all organisms isolated from hospital patients. One of the few antibiotics introduced in recent years (2007) is *doripenem,* a carbapenem. It's especially useful against *Pseudomomas aeruginosa* infections.

Monobactams

Another method of avoiding the effects of penicillinase is shown by *aztreonam*, which is the first member of a new class of antibiotics. It's a synthetic antibiotic that has only a single ring rather than the conventional β-lactam double ring, and it's therefore known as a **monobactam.** Aztreonam's spectrum of activity is remarkable for a penicillin-related compound—this antibiotic, which has unusually low toxicity, affects only certain gram-negative bacteria, including pseudomonads and *E. coli.*

Cephalosporins

In structure, the nuclei of **cephalosporins** resemble those of penicillin (Figure 20.9). Cephalosporins inhibit cell wall synthesis in essentially the same way as do penicillins. They are more widely used than any other β-lactam antibiotics. Their β-lactam ring differs slightly from that of penicillin, but bacteria have developed β-lactamases that inactivate them.

Cephalosporins are most commonly grouped according to their generations, reflecting their continued development, as described in Table 20.4.

Polypeptide Antibiotics

Bacitracin *Bacitracin* (the name is derived from its source, a *Bacillus* isolated from a wound on a girl named *Tracy*) is a polypeptide antibiotic effective primarily against gram-positive bacteria, such as staphylococci and streptococci. Bacitracin inhibits the synthesis of cell walls at an earlier stage than penicillins and cephalosporins. It interferes with the synthesis of the linear strands of the peptidoglycans (see Figure 4.13a). Its use is restricted to topical application for superficial infections.

Vancomycin *Vancomycin* (optimistically named from the word *vanquish*) is one of a small group of glycopeptide antibiotics derived from a species of *Streptomyces* found in the jungles of Borneo. Originally, toxicity of vancomycin was a serious problem, but improved purification procedures in its manufacture have largely corrected this. Although it has a very narrow spectrum of activity, which is based on inhibition of cell wall synthesis, vancomycin has been extremely important in addressing the problem of MRSA (see page 411). Vancomycin has been considered the last line of antibiotic defense for treatment of

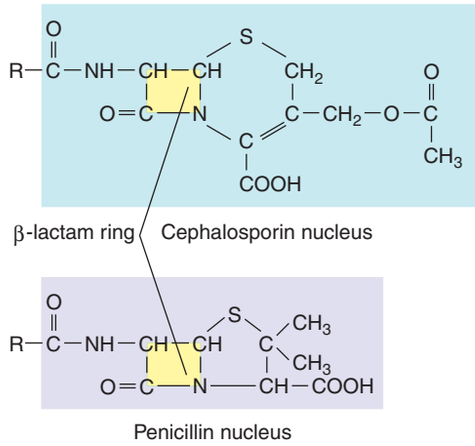


Figure 20.9 The nuclear structures of cephalosporin and penicillin compared.

Would a β-lactamase effective against penicillin G be likely to affect cephalosporins?

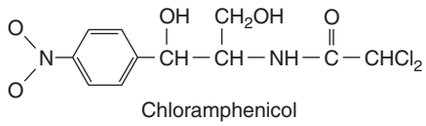
Staphylococcus aureus infections that are resistant to other antibiotics. The widespread use of vancomycin to treat MRSA has led to the appearance of **vancomycin-resistant enterococci (VRE).** These are opportunistic, gram-positive pathogens that are particularly troublesome in hospital settings. (See Chapter 14's section on healthcare-associated infections on page 402 and the Clinical Focus box on page 573.) This appearance of vancomycin-resistant pathogens, leaving few effective alternatives, is considered a medical emergency. Telavancin, a semisynthetic derivative of vancomycin, has been introduced and approved for a limited range of uses.

Antimycobacterial Antibiotics

The cell wall of members of the genus *Mycobacterium* differs from the cell wall of most other bacteria. It incorporates mycolic acids that are a factor in their staining properties, causing them to stain as acid-fast (page 83). The genus includes important pathogens, such as those that cause leprosy and tuberculosis.

Isoniazid (INH) is a very effective synthetic antimicrobial drug against *Mycobacterium tuberculosis.* The primary effect of INH is to inhibit the synthesis of mycolic acids, which are components of cell walls only of the mycobacteria. It has little effect on nonmycobacteria. When used to treat tuberculosis, INH is usually administered simultaneously with other drugs, such as rifampin or ethambutol. This minimizes development of drug resistance. Because the tubercle bacillus is usually found only within macrophages or walled off in tissue, any antitubercular drug must be able to penetrate into such sites.

Ethambutol is effective only against mycobacteria. The drug apparently inhibits incorporation of mycolic acid into the



Chloramphenicol

Figure 20.10 The structure of the antibacterial antibiotic chloramphenicol. Notice the simple structure, which makes synthesizing this drug less expensive than isolating it from *Streptomyces*.

Q What effect does the binding of chloramphenicol to the 50S portion of the ribosomes have on a cell?

cell wall. It's a comparatively weak antitubercular drug; its principal use is as the secondary drug to avoid resistance problems.

CHECK YOUR UNDERSTANDING

- One of the most successful groups of antibiotics targets the synthesis of bacterial cell walls; why does the antibiotic not affect the mammalian cell? **20-6**
- What phenomenon prompted the development of the first semisynthetic antibiotics, such as methicillin? **20-7**
- What genus of bacteria has mycolic acids in the cell wall? **20-8**

Inhibitors of Protein Synthesis

Chloramphenicol

Chloramphenicol inhibits the formation of peptide bonds in the growing polypeptide chain by reacting with the 50S portion of the 70S prokaryotic ribosome. Because of its simple structure (**Figure 20.10**), it is less expensive for the pharmaceutical industry to synthesize it chemically than to isolate it from *Streptomyces*. It is relatively inexpensive, and has a broad spectrum, so chloramphenicol is often used where low cost is essential. Its small molecular size promotes diffusion into areas of the body that are inaccessible to many other drugs. However, chloramphenicol has serious adverse effects that include suppression of bone marrow activity. This affects the formation of blood cells. Physicians are advised not to use the drug for trivial conditions or if suitable alternatives are available.

Other antibiotics that inhibit protein synthesis by binding at the same ribosomal site as chloramphenicol are *clindamycin* and *metronidazole* (see page 567). These three drugs are structurally unrelated, but all have potent anaerobic activity. Clindamycin has a noted association with *Clostridium difficile*–associated diarrhea (see page 724). Its effectiveness against anaerobes has led to its use in the treatment of acne.

Aminoglycosides

Aminoglycosides are a group of antibiotics in which amino sugars are linked by glycoside bonds. Aminoglycoside antibiotics interfere with the initial steps of protein synthesis by changing the shape of the 30S portion of the 70S prokaryotic ribosome. This interference causes the genetic code of the mRNA to be read incorrectly. They were among the first antibiotics to have significant activity against gram-negative bacteria. Probably the best-known aminoglycoside is *streptomycin,* which was discovered in 1944. Streptomycin is still used as an alternative drug in the treatment of tuberculosis, but rapid development of resistance and serious toxic effects have diminished its usefulness.

Aminoglycosides can affect hearing by causing permanent damage to the auditory nerve, and damage to the kidneys has also been reported. As a result, their use has been declining. *Neomycin* is present in many nonprescription topical preparations. *Gentamicin* (spelled with an "i" to reflect its source, the filamentous bacterium *Micromonospora*) is especially useful against *Pseudomonas* infections. Pseudomonads are a major problem for persons suffering from cystic fibrosis. The aminoglycoside *tobramycin* is administered in an aerosol to help control infections that occur in patients with cystic fibrosis.

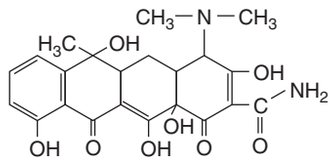
Tetracyclines

Tetracyclines are a group of closely related broad-spectrum antibiotics produced by *Streptomyces* spp. The tetracyclines interfere with the attachment of the tRNA carrying the amino acids to the ribosome at the 30S portion of the 70S ribosome, preventing the addition of amino acids to the growing polypeptide chain. They do not interfere with mammalian ribosomes because they do not penetrate very well into intact mammalian cells. However, at least small amounts are able to enter the host cell, as is apparent from the fact that the intracellular pathogenic rickettsias and chlamydias are sensitive to tetracyclines. The selective toxicity of these drugs is due to the greater sensitivity of the bacteria at the ribosomal level. Tetracyclines not only are effective against gram-positive and gram-negative bacteria but also penetrate body tissues well and are especially valuable against the intracellular rickettsias and chlamydias. Three of the more commonly used tetracyclines are *oxytetracycline*

Clinical Case

Dr. Singh asks the eye bank for more information about the donor. She finds out that the cornea donor was a previously healthy 30-year-old victim of a motorcycle crash who was on ventilator support for 4 days before his death. The donor's corneas were harvested 3 days before the transplantations took place and were stored in a buffered medium containing 100 µg/mL gentamicin at 4°C.

How would you determine susceptibility of this *P. aeruginosa* to gentamicin?



Tetracycline

Figure 20.11 The structure of the antibacterial antibiotic tetracycline. Other tetracycline-type antibiotics share the four-cyclic-ring structure of tetracycline and closely resemble it.

Q How do tetracyclines affect bacteria?

(Terramycin), *chlortetracycline* (Aureomycin), and tetracycline itself (**Figure 20.11**).

Some semisynthetic tetracyclines, such as *doxycycline* and *minocycline,* are available. They have the advantage of longer retention in the body.

Tetracyclines are used to treat many urinary tract infections, mycoplasmal pneumonia, and chlamydial and rickettsial infections. They are also frequently used as alternative drugs for such diseases as syphilis and gonorrhea. Because of their broad spectrum, tetracyclines often suppress the normal intestinal microbiota, causing gastrointestinal upsets, often leading to superinfections, particularly by the fungus *Candida albicans.* They are not advised for children, who might experience a brownish discoloration of the teeth, or for pregnant women, in whom they might cause liver damage. Tetracyclines are among the most common antibiotics added to animal feeds, where their use results in significantly faster weight gain; however, some human health problems can also result (see the Clinical Focus box on page 573).

Glycylcyclines

The glycylcyclines are a newer class of antibiotics discovered since 2000. They are structurally similar to the tetracyclines. The best-known example is *tygecycline (Tygacil).* This is a broad-spectrum, bacteriostatic antibiotic that binds to the 30S ribosomal subunit, blocking protein synthesis. An important advantage is that it inhibits the effects of rapid efflux, an important mechanism for bacterial antibiotic resistance (see page 571). Among its disadvantages is that it must be administered by slow intravenous infusion. It is especially useful against MRSA and multi-drug-resistant strains of *Acinetobacter baumanii.*

Macrolides

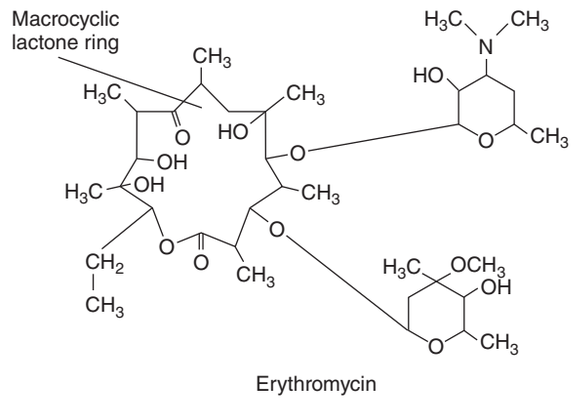
Macrolides are a group of antibiotics named for the presence of a macrocyclic lactone ring. The best-known macrolide in clinical use is *erythromycin* (**Figure 20.12**). Its mode of action is the inhibition of protein synthesis, apparently by blocking the tunnel shown in Figure 20.4a. However, erythromycin is not able to penetrate the cell walls of most gram-negative bacilli. Its spectrum of activity is therefore similar to that of penicillin G, and it is a frequent alternative drug to penicillin. Because it can be administered orally, an orange-flavored preparation of erythromycin is a frequent substitute for penicillin in treating streptococcal and staphylococcal infections in children. Erythromycin is also the drug of choice for the treatment of legionellosis, mycoplasmal pneumonia, and several other infections.

A member of a new class of macrocyclic antibiotics is fidaxomicin. It has a rather narrow spectrum of activity and is mainly used to treat *Clostridium difficile* and clostridia infections. It is a frequent replacement for vancomycin. Other macrolides now available include *azithromycin* and *clarithromycin.* Compared to erythromycin, they have a broader antimicrobial spectrum and penetrate tissues better. This is especially important in the treatment of conditions caused by intracellular bacteria such as *Chlamydia,* a frequent cause of sexually transmitted infection.

A new generation of semisynthetic macrolides, the **ketolides,** is being developed to cope with increasing resistance to other macrolides. The prototype of this generation is *telithromycin* (Ketek). However, it has a number of significant restrictions related to toxicity.

Streptogramins

We mentioned previously that the appearance of vancomycin-resistant pathogens constitutes a serious medical problem. One answer may be a unique group of antibiotics, the **streptogramins.** The first of these drugs to be released, Synercid, is a combination of two cyclic peptides, *quinupristin* and *dalfopristin,* which are distantly related to the macrolides. They block protein synthesis by attaching to the 50S portion of the ribosome, as do other antibiotics such as chloramphenicol. Synercid, however, acts at uniquely different points on the ribosome. Dalfopristin blocks an early step in protein synthesis, and quinupristin blocks a later step. The combination causes incomplete peptide



Erythromycin

Figure 20.12 The structure of the antibacterial antibiotic erythromycin, a representative macrolide. All macrolides have the macrocyclic lactone ring shown here.

Q How do macrolides affect bacteria?

chains to be released and is synergistic in its action (see page 574). Synercid is effective against a broad range of gram-positive bacteria that are resistant to other antibiotics. This makes Synercid especially valuable, even though it's expensive and has a high incidence of adverse side effects.

Oxazolidinones

The oxazolidinones are another new class of antibiotics developed in response to vancomycin resistance. When the FDA approved this class of antibiotic in 2001, it represented the first new class of antibiotics to come to market in 25 years. Like several other antibiotics that inhibit protein synthesis, oxazolidinone antibiotics act on the ribosome (see Figure 20.4). However, they are unique in their target, binding to the 50S ribosomal subunit close to the point where it interfaces with the 30S subunit. These drugs are totally synthetic, which may make resistance slower to develop. One member of this antibiotic group is *linezolid* (Zyvox), used mainly to combat MRSA.

Pleuromutilins

Pleuromutilin derivatives and the oxazolidinones represent two of the new classes of antibiotics developed since 2000 (also see the following discussion of lipopeptides). They have a unique mode of action that interferes with protein synthesis. The first antibiotic of this class approved for human use is retapamulin. It was, however, limited to only topical use. They are effective against gram-positive bacteria. Originally a product of the *Pleurotis mutilus* mushroom, most are now semisynthetic derivatives.

CHECK YOUR UNDERSTANDING

- Why does erythromycin, a macrolide antibiotic, have activity limited largely to gram-positive bacteria even though its mode of action is similar to that of the broad-spectrum tetracyclines? **20-9**

Injury to the Plasma Membrane

The synthesis of bacterial plasma membranes requires the synthesis of fatty acids as building blocks. Researchers in search of an attractive target for new antibiotics have focused their attention on this metabolic step, which is distinct from the fatty acid biosynthesis in humans. Interference with this process is the basis of several antibiotics and antimicrobials. A weakness in this approach, however, is that many bacterial pathogens are able to take up fatty acids from serum. In the soil environment from which the antibiotic-producing streptomycetes were isolated, fatty acids are not available. Examples of successful antimicrobials that target fatty acid synthesis are the tuberculosis drug *isoniazid* (page 559) and the household antibacterial *triclosan* (page 188).

Lipopeptides

A **lipopeptide** antibiotic effective only against gram-positive bacteria is *daptomycin* (Cubicin), produced by a streptomycete. Its use is approved for certain skin infections. The apparent mechanism of action is to attack the membrane of the bacterial cell, and resistance is uncommon. This mechanism is distinctive enough that the antibiotic is often used when the infection is caused by bacteria resistant to numerous antibiotics.

Polymyxin B is a bactericidal antibiotic effective against gram-negative bacteria. For many years it was one of very few drugs available for use against infection by *Pseudomonas* bacteria. It's seldom used today except in the topical treatment of superficial infections, for which it's available in nonprescription antiseptic ointments.

Both *bacitracin* and *polymyxin B* are available in nonprescription antiseptic ointments, in which they are usually combined with *neomycin,* a broad-spectrum aminoglycoside. In a rare exception to the rule, these antibiotics do not require a prescription.

Many of the antimicrobial peptides discussed on page 575 target the synthesis of the plasma membrane.

CHECK YOUR UNDERSTANDING

- Of the three drugs often found in over-the-counter antiseptic creams—polymyxin B, bacitracin, and neomycin—which has a mode of action most similar to that of penicillin? **20-10**

Nucleic Acid Synthesis Inhibitors

Rifamycins

The best-known derivative of the **rifamycin** family of antibiotics is *rifampin.* These drugs are structurally related to the macrolides and inhibit the synthesis of mRNA. By far the most important use of rifampin is against mycobacteria in the treatment of tuberculosis and leprosy. A valuable characteristic of rifampin is its ability to penetrate tissues and reach therapeutic levels in cerebrospinal fluid and abscesses. This characteristic is probably an important factor in its antitubercular activity, because the tuberculosis pathogen is usually located inside tissues or macrophages. An unusual side effect of rifampin is the appearance of orange-red urine, feces, saliva, sweat, and even tears.

Quinolones and Fluoroquinolones

In the early 1960s, the synthetic drug *nalidixic acid* was developed—the first of the **quinolone** group of antimicrobials. It exerted a unique bactericidal effect by selectively inhibiting an enzyme (DNA gyrase) needed for the replication of DNA. Although nalidixic acid found only limited use (its only application is for urinary tract infections), it led to the development in the 1980s of a prolific group of synthetic quinolones, the **fluoroquinolones.**

The fluoroquinolones are divided into groups, each of which has a progressively broader spectrum of activity. The earliest generations include widely used *norfloxacin* and *ciprofloxacin.* The latter is better known under its trade name of Cipro and is best known for its use against anthrax infections. A newer group of

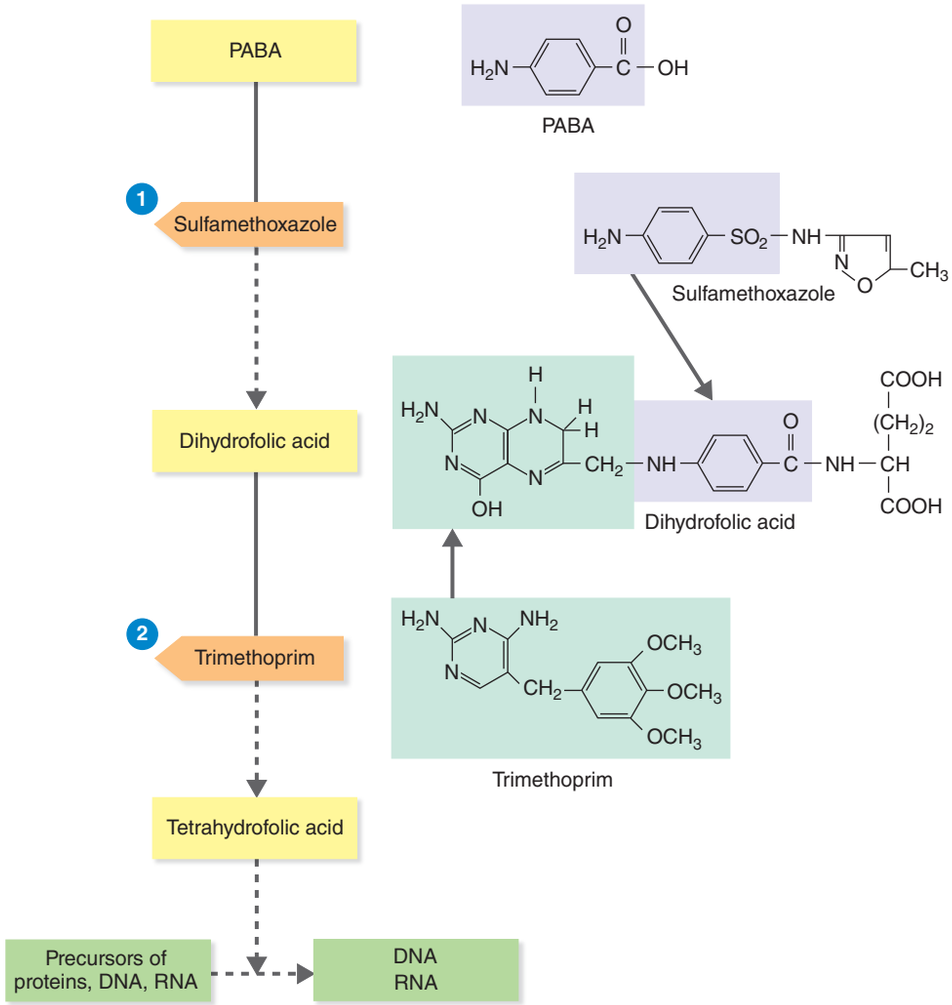


Figure 20.13 Actions of the antibacterial synthetics trimethoprim and sulfamethoxazole. TMP-SMZ works by inhibiting different stages in the synthesis of precursors of DNA, RNA, and proteins. Together the drugs are synergistic.

1. Sulfamethoxazole, a sulfonamide that is a structural analog of PABA, competitively inhibits the synthesis of dihydrofolic acid from PABA.
2. Trimethoprim, a structural analog of a portion of dihydrofolic acid, competitively inhibits the synthesis of tetrahydrofolic acid.

Define *synergism.*

fluoroquinolones includes *gemifloxacin* and *moxifloxacin.* These antibiotics, with the exception of moxifloxacin, are often the drugs of choice for urinary tract infections and certain types of pneumonia. As a group, the fluoroquinolones are relatively nontoxic. Resistance to them can develop rapidly, even during a course of treatment.

CHECK YOUR UNDERSTANDING

What group of antibiotics interferes with the DNA-replicating enzyme DNA gyrase? **20-11**

Competitive Inhibition of Essential Metabolites

Blocking a cell's ability to synthesize essential metabolites is another mode of drug action.

Sulfonamides

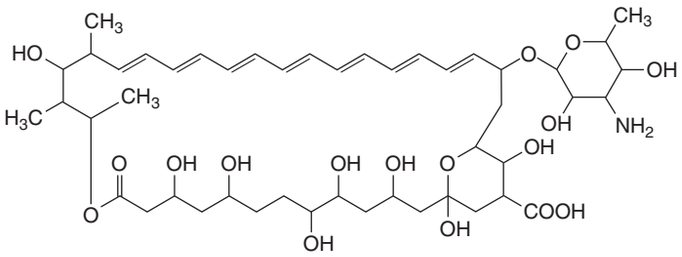
As noted earlier, **sulfonamides,** or **sulfa drugs,** were some of the first antimicrobial therapies created. Folic acid is an important coenzyme needed for synthesis of proteins, DNA, and RNA. Sulfa drugs are structurally similar to a folic acid precursor called *para-aminobenzoic acid* (PABA), allowing them to competitively bind with the enzyme meant for PABA and thereby block folic acid production. The drugs are bacteriostatic and do not harm human cells because we take up folic acid from our diet rather than synthesize it.

A combination of *trimethoprim* and *sulfamethoxazole* (TMP-SMZ) is widely used today. **Figure 20.13** shows its mode of action. Only 10% of the combined concentration is needed compared to when the drugs are used separately—an example of drug **synergism.** The combination also has a broader spectrum of action and greatly reduces emergence of resistant strains.

Antibiotics have diminished the importance of sulfa drugs. However, they continue to be effective treatments for certain urinary tract infections, and the drug silver sulfadiazine is also used to control infections in burn patients.

CHECK YOUR UNDERSTANDING

Both humans and bacteria need PABA to make folic acid, so why do sulfa drugs adversely impact only bacterial cells? **20-12**



Amphotericin B

Figure 20.14 The structure of the antifungal drug amphotericin B, representative of the polyenes.

Q Why do polyenes injure fungal plasma membranes and not bacterial membranes?

Antifungal Drugs

Eukaryotes, such as fungi, use the same mechanisms to synthesize proteins and nucleic acids as higher animals. Therefore it's more difficult to find a point of selective toxicity in eukaryotes than in prokaryotes. Moreover, fungal infections are becoming more frequent because of their role as opportunistic infections in immunosuppressed individuals, especially those with AIDS.

Agents Affecting Fungal Sterols

Many antifungal drugs target the sterols in the plasma membrane. In fungal membranes, the principal sterol is ergosterol; in animal membranes, cholesterol. When the biosynthesis of ergosterol in a fungal membrane is interrupted, the membrane becomes excessively permeable, killing the cell. Inhibition of ergosterol biosynthesis is the basis for the selective toxicity of many antifungals, which include members of the polyene, azole, and allylamine groups.

Polyenes *Amphotericin B* is the most commonly used member of the antifungal **polyene antibiotics** (Figure 20.14). For many years amphotericin B, produced by *Streptomyces* species of soil bacteria, has been a mainstay of clinical treatment for systemic fungal diseases such as histoplasmosis, coccidioidomycosis, and blastomycosis. The drug's toxicity, particularly to the kidneys, is a strongly limiting factor in these uses. Administering the drug encapsulated in lipids (*liposomes*) appears to minimize toxicity.

Azoles Some of the most widely used antifungal drugs are represented among the **azole antibiotics.** Before they made their appearance, the only drugs available for systemic fungal infections were amphotericin B and flucytocine (discussed later). The first azoles were **imidazoles,** such as *clotrimazole* and *miconazole* (Figure 20.15), which are now sold without a prescription for topical application for treatment of cutaneous mycoses, such as athlete's foot and vaginal yeast infections. An important addition to this group was *ketoconazole*, which has an unusually broad spectrum of activity among fungi. Ketoconazole, taken orally, proved to be an alternative to amphotericin B for many systemic fungal infections. Ketoconazole topical ointments are used to treat dermatomycoses of the skin.

The use of ketoconazole for systemic infections diminished when the less toxic **triazole** antifungal antibiotics were introduced. The original drugs of this type were *fluconazole* and *itraconazole*. They are much more water soluble, making them easier to use and more effective against systemic infections. The triazole group has recently expanded since the introduction of *voriconazole,* which has become the new standard for treatment of *Aspergillus* infections in immunocompromised patients. The newest triazole drug to be approved is *posaconazole,* which will probably be used to treat a number of systemic fungal infections.

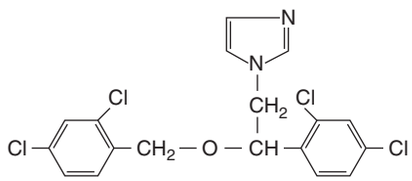
Allylamines The **allylamines** represent a class of antifungals that inhibit the biosynthesis of ergosterols in a manner that is functionally distinct. *Terbinafine* and *naftifine,* examples of this group, are frequently used when resistance to azole-type antifungals arises.

Agents Affecting Fungal Cell Walls

The fungal cell wall contains compounds unique to these organisms. Other than ergosterol, a primary target for selective toxicity among these compounds is β-glucan. A new class of antifungal drugs is the **echinocandins,** which inhibit the biosynthesis of glucans, resulting in an incomplete cell wall and cell lysis. A member of the echinocandin group, *caspofungin* (Cancidas), is expected to become especially valuable for combating systemic *Aspergillus* infections in persons whose immune systems are compromised. It's also effective against important fungi such as *Candida* spp.

Agents Inhibiting Nucleic Acids

Flucytosine, an analog of the pyrimidine cytosine, interferes with the biosynthesis of RNA and therefore protein synthesis. The selective toxicity lies in the ability of the fungal cell to convert flucytocine into 5-fluorouracil, which is incorporated into



Miconazole

Figure 20.15 The structure of the antifungal drug miconazole, representative of the imidazoles.

Q How do azoles affect fungi?

RNA and eventually disrupts protein synthesis. Mammalian cells lack the enzyme to make this conversion of the drug. Flucytosine has a narrow spectrum of activity, and toxicity to the kidneys and bone marrow further limit its use.

Other Antifungal Drugs

Griseofulvin is an antibiotic produced by a species of *Penicillium*. It has the interesting property of being active against superficial dermatophytic fungal infections of the hair (tinea capitis, or ringworm) and nails, even though its route of administration is oral. The drug apparently binds selectively to the keratin found in the skin, hair follicles, and nails. Its mode of action is primarily to block microtubule assembly, which interferes with mitosis and thereby inhibits fungal reproduction.

Tolnaftate is a common alternative to miconazole as a topical agent for the treatment of athlete's foot. Its mechanism of action isn't known. *Undecylenic acid* is a fatty acid that has antifungal activity against athlete's foot, although it isn't as effective as tolnaftate or the imidazoles.

Pentamidine is used in treating *Pneumocystis* pneumonia, a frequent complication of AIDS. It also is useful in treating several protozoan-caused tropical diseases. The drug's mode of action is unknown, but it appears to bind to DNA.

CHECK YOUR UNDERSTANDING

What sterol in the cell membrane of fungi is the most common target for antifungal action? **20-13**

Antiviral Drugs

In developed parts of the world, it's estimated that at least 60% of infectious illnesses are caused by viruses, and about 15% by bacteria. Every year, at least 90% of the U.S. population suffers from a viral disease. Even so, compared to the number of antibiotics available for treating bacterial diseases, there are relatively few antiviral drugs. Many of the recently developed antiviral drugs are directed against HIV, the pathogen responsible for the pandemic of AIDS. Therefore, as a practical matter the discussion of antivirals is often separated into agents that are directed at HIV (see pages 566–567 and 542–543) and those for other infections, such as influenza, herpes, and hepatitis (see Table 20.5).

Because viruses replicate within the host's cells, very often using the genetic and metabolic mechanisms of the host's own cells, it's relatively difficult to target the virus without damaging the host's cellular machinery. Many of the antivirals in use today are analogs of components of viral DNA or RNA. However, as more becomes known about the reproduction of viruses, more targets suggest themselves for antiviral action.

Entry and Fusion Inhibitors

Drugs that block the initial steps in viral infection—absorption and penetration—are entry inhibitors. Several entry inhibitors are approved to treat HIV. Entry inhibitors target the receptors that HIV uses to bind to the cell before entry, such as CCR5 (see Figure 19.13, page 535). The first of this class of drugs to target HIV infection step is *maraviroc*. Entry of HIV into the cell can also be blocked by fusion inhibitors, such as *enfuvirtide*. This is a synthetic peptide that blocks fusion of the virus and cell by mimicking a region of the gp41 HIV-1 envelope (again, see Figure 19.13).

Uncoating, Genome Integration, and Nucleic Acid Synthesis Inhibitors

Prior to the start of viral replication, viral nucleic acids are released from their protein coat. Drugs that prevent this uncoating include anti–influenza A drugs *amantadine* and *rimantadine*. Once the virus has entered the cell and uncoated, the nucleic acids are free within the host cell. In order for HIV to replicate, the viral DNA must integrate into the genome of the host cell. This requires the enzyme integrase. Drugs such as *raltegravir* and *elvitegravir* are competitive inhibitors of integrase.

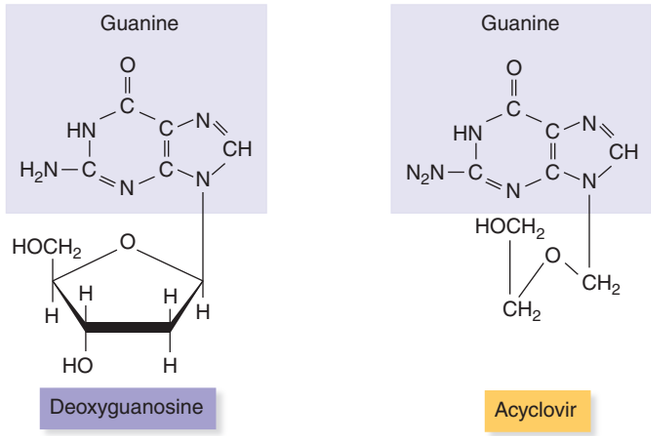
Nucleic acid synthesis is an important target for antivirals, especially for the treatment of HIV and herpes infections. Many of these drugs are analogs of nucleic acids (page 45), which inhibit RNA or DNA synthesis once the analog is incorporated. Others are non-nucleoside peptides that bind a viral enzyme, resulting in allosteric inhibition. An obvious target for nucleic acid inhibition is the enzyme reverse transcriptase, used by HIV and hepatitis B virus during synthesis of DNA, because this step is not used in human DNA synthesis (page 247 and Figure 9.9). A nucleoside analog, *acyclovir* is used for treating herpes infections, especially genital herpes. It's an especially useful treatment in immunosuppressed individuals. Acyclovir is selectively used by the viral enzyme thymidine kinase (**Figure 20.16**). The drugs *famciclovir* and *ganciclovir* are derivatives of acyclovir and have a similar mode of action. *Ribavirin* resembles the nucleoside guanine and accelerates the already high mutation rate of RNA viruses until the accumulation of errors reaches a crisis point, killing the virus. More recently, a nucleotide analog *adefovir dipivoxil* (Hepsera) has been introduced for patients whose infections are resistant to lamivudine. Another nucleoside analog, *cidofovir,* is currently used to treat cytomegalovirus infection of the eye.

Interference with Assembly and Release of Viral Particles

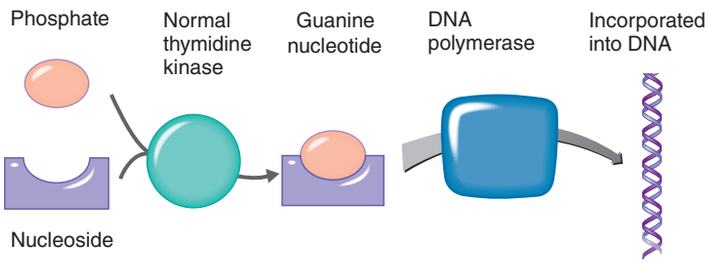
The production of infectious viral particles requires an important group of enzymes called proteases. Viral replication requires the enzymatic cleavage of protein precursors. Some drugs, called **protease inhibitors,** block this step. Examples are *saquinavir* for HIV and *boceprevir* and *telaprevir* for hepatitis C infections.

Exit Inhibitors

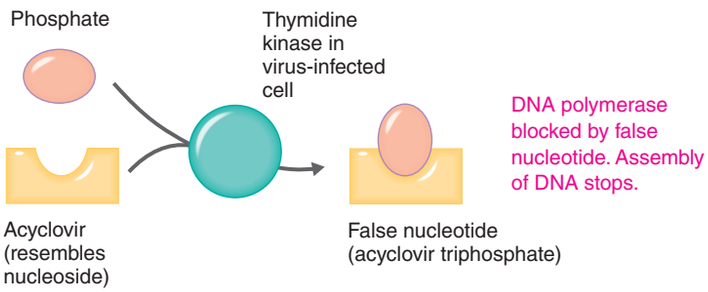
In order for a virus to reproduce, it must bud from the host cell. For influenza viruses, this requires the enzyme neuraminidase (page 695). Currently there are two drugs that are competitive inhibitors of this enzyme, allowing them to block release of



(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.



(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) to a false nucleotide, which blocks DNA synthesis by DNA polymerase.

Figure 20.16 The structure and function of the antiviral drug acyclovir.

Q Why are viral infections generally difficult to treat with chemotherapeutic agents?

viral particles. They are *zanamivir* (Relenza), taken by inhalation, and *oseltamivir* (Tamiflu), taken orally.

Interferons

Cells infected by a virus often produce interferon, which inhibits further spread of the infection. Interferons are classified as cytokines, discussed in Chapter 17. *Alpha interferon* (see Chapter 16, page 460) is currently a drug of choice for viral hepatitis infections. The production of interferons can be stimulated by a recently introduced antiviral, *imiquimod.* This drug is often prescribed to treat genital warts.

CHECK YOUR UNDERSTANDING

One of the most widely used antivirals, acyclovir, inhibits the synthesis of DNA. Humans also synthesize DNA, so why is the drug still useful in treating viral infections? **20-14**

Antivirals for Treating HIV/AIDS

The interest in effective treatments for the pandemic of HIV infections requires a separate discussion of the many antiviral drugs developed for this. HIV is an RNA virus, and its reproduction depends on the enzyme reverse transcriptase, which controls the synthesis of RNA from DNA (see page 378). In fact, the term **antiretroviral** currently implies that a drug is used to treat HIV infections (see the discussion of HAART on page 543). A well-known example of a ***nucleoside* analog** is *zidovudine.* An example of a ***nucleotide* analog** is *tenofovir.* In consideration of the large number of drugs required to treat HIV, especially to minimize development of resistant strains, combinations of drugs have been developed. An example is Atripla, which combines *tenofovir, emtricitabine,* and *efavirenz.*

Not all drugs that inhibit reverse transcriptase are nucleoside or nucleotide analogs. For example, a few **non-nucleoside inhibitors,** such as *nevirapine,* block RNA synthesis by other mechanisms.

As the reproduction of HIV became better understood, other approaches to its control became available. When the host cell (at the direction of the infecting HIV) makes a new virus, it must begin by cutting up large proteins with protease enzymes. The resulting fragments are then used to assemble new viruses. Analogs of amino acid sequences in the large proteins can serve as inhibitors of these proteases by competitively interfering with their activity. The protease inhibitors *atazanavir, indinavir,* and *saquinavir* have proved especially effective when combined with inhibitors of reverse transcriptase.

Drugs that use new targets of HIV reproduction are being considered, and several are undergoing clinical tests. Among these are integrase inhibitors, which inhibit an enzyme that integrates viral DNA into the DNA of the infected cell. The first of this new class of HIV antivirals to be approved is *raltegravir*.

Viral infection obviously requires entry into the cell. Entry inhibitors include antivirals that target the receptors that HIV uses to bind to the cell before entry, such as CCR5 (see Figure 19.13, page 535). The first of a class of drugs that target this infection step is *maraviroc*. Entry of HIV into the cell can also be blocked by fusion inhibitors such as *enfuvirtide*. This is a synthetic peptide that blocks cell fusion and entry by mimicking a

region of the gp41 HIV-l envelope (again, see Figure 19.13). It is, however, dauntingly expensive and must be injected twice daily.

Antiprotozoan and Antihelminthic Drugs

For hundreds of years, quinine from the bark of the cinchona tree was the only drug known to be effective for treating a parasitic infection. Peruvian natives had observed that quinine, which is an effective muscle relaxant, controlled the shivering symptomatic of malarial fever. Actually, this characteristic is unrelated to quinine's toxicity to the protozoan that causes malaria. It was first introduced into Europe in the early 1600s and was known as "Jesuit's powder." There are now many antiprotozoan and antihelminthic drugs, although many of them are still considered experimental. This doesn't preclude their use, however, by qualified physicians. The Centers for Disease Control and Prevention (CDC) provides several of them on request when they aren't available commercially.

Antiprotozoan Drugs

Quinine is still used to control the protozoan disease malaria, but synthetic derivatives, such as *chloroquine,* have largely replaced it. For preventing malaria in areas where the disease has developed resistance to chloroquine, the new drug *mefloquine* (Lariam) is often recommended, although serious psychiatric side effects have been reported.

As resistance to the most widely used and cheapest drug, chloroquine, becomes almost universal, the products of a Chinese shrub, *artemisinin* and *artemisinin-based combination therapies (ACTs),* have become the principal treatment of malaria. Artemisinin was a traditional Chinese medicine long used for controlling fevers: Chinese scientists, following this lead, identified its antimalarial properties in 1971. ACTs act by killing the asexua1 stages of *Plasmodium* spp. in the blood (Figure 12.20 on page 341), and they also affect the sexual stages that transmit the infection by mosquitoes. Compared to choroquinine, ACTs are expensive—a problem in malaria-prone areas. This has led to widespread distribution of low-cost, but ineffective, counterfeit ACTs. Some of these contain enough of the genuine drug to evade simple tests, but these low dosages are accelerating development of resistance.

Quinacrine is the drug of choice for treating the protozoan disease giardiasis. *Diiodohydroxyquin (iodoquinol)* is an important drug prescribed for several intestinal amebic diseases, but its dosage must be carefully controlled to avoid optic nerve damage.

Metronidazole (Flagyl) is one of the most widely used antiprotozoan drugs. It's unique in that it acts not only against parasitic protozoa but also against obligately anaerobic bacteria. For example, as an antiprotozoan agent, it's the drug of choice for vaginitis caused by *Trichomonas vaginalis.* It's also used in treating giardiasis and amebic dysentery. The mode of action is to interfere with anaerobic metabolism, which incidentally these protozoans share with certain obligately anaerobic bacteria, such as *Clostridium.*

Tinidazole, a drug similar to metronidazole, is effective in treating giardiasis, amebiasis, and trichomoniasis. Another antiprotozoan agent, and the first to be approved for the chemotheraphy of diarrhea caused by *Cryptosporidium hominis,* is *nitazoxanide.* It's active in treating giardiasis and amebiasis. Interestingly, it's also effective in treating several helminthic diseases, as well as having activity against some anaerobic bacteria.

Antihelminthic Drugs

With the increased popularity of sushi, a Japanese specialty often made with raw fish, the CDC began to notice an increased incidence of tapeworm infections. To estimate the incidence, the CDC documents requests for *niclosamide,* which is the usual first choice in treatment. The drug is effective because it inhibits ATP production under aerobic conditions. *Praziquantel* is about equally effective for the treatment of tapeworms; it kills worms by altering the permeability of their plasma membranes. Praziquantel has a broad spectrum of activity and is highly recommended for treating several fluke-caused diseases, especially schistosomiasis. It causes the helminths to undergo muscular spasms and also makes them susceptible to attack by the immune system. Apparently, its action exposes surface antigens, which antibodies can then reach.

Mebendazole and *albendazole* are broad-spectrum antihelminthics that have few side effects and have become the drugs of choice for treating many intestinal helminthic infections. Both drugs inhibit the formation of microtubules in the cytoplasm, which interferes with the absorption of nutrients by the parasite. These drugs are also widely used in the livestock industry; for veterinary applications, they are relatively more effective in ruminant animals.

Ivermectin is a drug with a wide range of applications. It's known to be produced by only one species of organism, *Streptomyces avermectinius,* which was isolated from the soil near a Japanese golf course. It's effective against many nematodes (roundworms) and several mites (such as scabies), ticks, and insects (such as head lice). (Some mites and insects happen to share certain similar metabolic channels with affected helminths.) Its primary use has been in the livestock industry as a broad-spectrum antihelminthic. Its exact mode of action is uncertain, but the final result is paralysis and death of the helminth without affecting mammalian hosts.

CHECK YOUR UNDERSTANDING

What was the first drug for parasitic infections? **20-15**

Tests to Guide Chemotherapy

LEARNING OBJECTIVE

20-16 Describe two tests for microbial susceptibility to chemotherapeutic agents.



Figure 20.17 The disk-diffusion method for determining the activity of antimicrobials. Each disk contains a different chemotherapeutic agent, which diffuses into the surrounding agar. The clear zones indicate inhibition of growth of the microorganism swabbed onto the agar surface.

Q Which agent is the most effective against the bacterium being tested?

Different microbial species and strains have different degrees of susceptibility to chemotherapeutic agents. Moreover, the susceptibility of a microorganism can change with time, even during therapy with a specific drug. Thus, a physician must know the sensitivities of the pathogen before treatment can be started. However, physicians often can't wait for sensitivity tests and must begin treatment based on their "best guess" estimation of the most likely pathogen causing the illness.

Several tests can be used to indicate which chemotherapeutic agent is most likely to combat a specific pathogen. However, if the organisms have been identified—for example, *Pseudomonas aeruginosa,* beta-hemolytic streptococci, or gonococci—certain drugs can be selected without specific testing for susceptibility. Tests are necessary only when susceptibility isn't predictable or when antibiotic resistance problems develop.

The Diffusion Methods

Probably the most widely used, although not necessarily the best, method of testing is the **disk-diffusion method,** also known as the *Kirby-Bauer test* (Figure 20.17). A Petri plate containing an agar medium is inoculated ("seeded") uniformly over its entire surface with a standardized amount of a test organism. Next, filter paper disks impregnated with known concentrations of chemotherapeutic agents are placed on the solidified agar surface. During incubation, the chemotherapeutic agents diffuse from the disks into the agar. The farther the agent diffuses from the disk, the lower its concentration. If the chemotherapeutic agent is effective, a **zone of inhibition** forms around the disk after a standardized incubation. The diameter of the zone can be measured; in general, the larger the zone, the more sensitive the microbe is to the antibiotic. The zone diameter is compared to a standard table for that drug and concentration, and the organism is reported as *sensitive, intermediate,* or *resistant.* For a drug with poor solubility, however, the zone of inhibition indicating that the microbe is sensitive will be smaller than for another drug that is more soluble and has diffused more widely. Results obtained by the disk-diffusion method are often inadequate for many clinical purposes. However, the test is simple and inexpensive and is most often used when more sophisticated laboratory facilities aren't available.

A more advanced diffusion method, the **E test,** enables a lab technician to estimate the **minimal inhibitory concentration (MIC),** the lowest antibiotic concentration that prevents visible bacterial growth. A plastic-coated strip contains a gradient of antibiotic concentrations, and the MIC can be read from a scale printed on the strip (Figure 20.18).

Broth Dilution Tests

A weakness of the diffusion method is that it doesn't determine whether a drug is bactericidal and not just bacteriostatic. A **broth dilution test** is often useful in determining the MIC and the **minimal bactericidal concentration (MBC)** of an antimicrobial drug. The MIC is determined by making a sequence of decreasing concentrations of the drug in a broth, which is then inoculated with the test bacteria (Figure 20.19). The wells that don't show growth (higher concentration than the MIC)

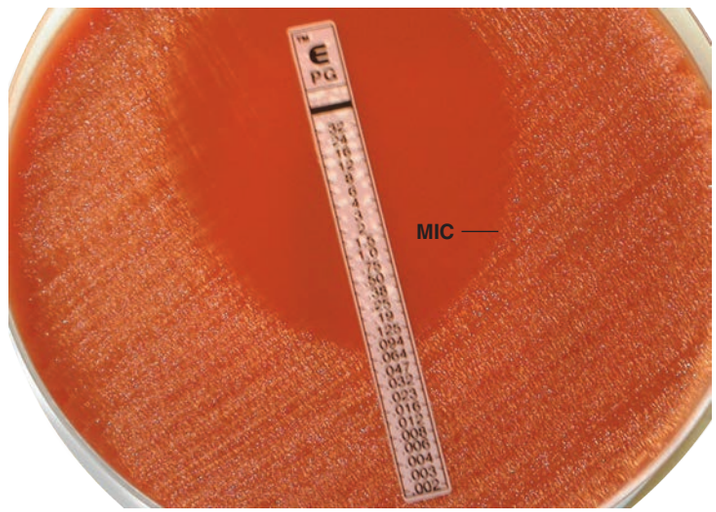


Figure 20.18 The E test (for epsilometer), a gradient diffusion method that determines antibiotic sensitivity and estimates minimal inhibitory concentration (MIC). The plastic strip, which is placed on an agar surface inoculated with test bacteria, contains an increasing gradient of the antibiotic. The MIC in µg/ml is clearly shown.

Q What is the MIC of this E test?

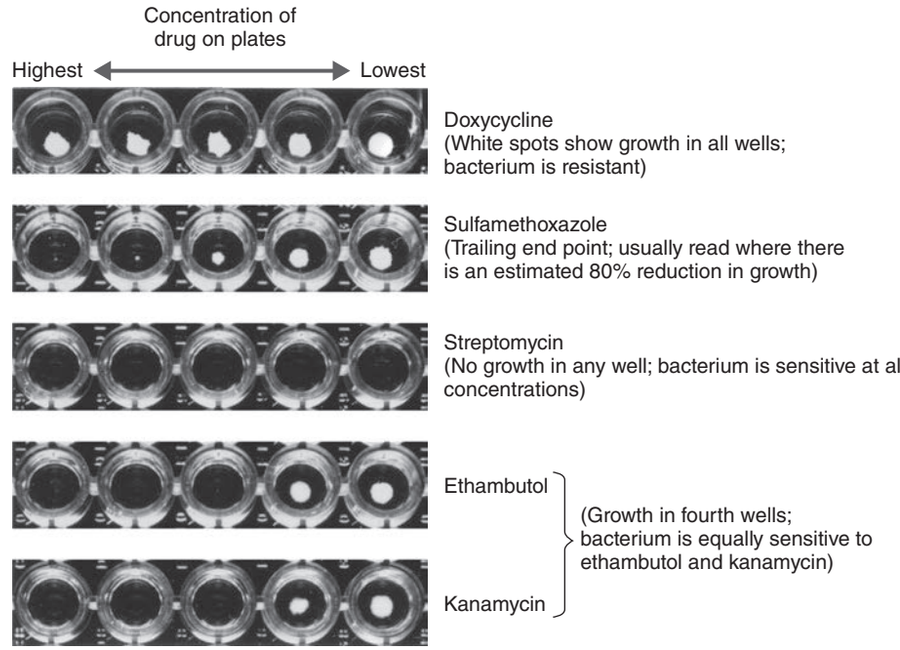


Figure 20.19 A microdilution, or microtiter, plate used for testing for minimal inhibitory concentration (MIC) of antibiotics. Such plates contain as many as 96 shallow wells that contain measured concentrations of antibiotics. They are usually purchased frozen or freeze dried (page 163). The test microbe is added simultaneously, with a special dispenser, to all the wells in a row of test antibiotics. To ensure that the microbe is capable of growth in the absence of the antibiotic, wells that contain no antibiotic are also inoculated (positive control). To ensure against contamination by unwanted microbes, wells that contain nutrient broth but no antibiotics or inoculum are included (negative control).

Q What is *MIC*?

can be cultured in broth or on agar plates free of the drug. If growth occurs in this broth, the drug was not bactericidal, and the MBC can be determined. Determining the MIC and MBC is important because it avoids the excessive or erroneous use of expensive antibiotics and minimizes the chance of toxic reactions that larger-than-necessary doses might cause.

Dilution tests are often highly automated. The drugs are purchased already diluted into broth in wells formed in a plastic tray. A suspension of the test organism is prepared and inoculated into all the wells simultaneously by a special inoculating device. After incubation, the turbidity may be read visually, although clinical laboratories with high workloads may read the trays with special scanners that enter the data into a computer that provides a printout of the MIC.

Other tests are also useful for the clinician; a determination of the microbe's ability to produce β-lactamase is one example. One popular, rapid method makes use of a cephalosporin that changes color when its β-lactam ring is opened. In addition, a measurement of the *serum concentration* of an antimicrobial is especially important when toxic drugs are used. These assays tend to vary with the drug and may not always be suitable for smaller laboratories.

The hospital personnel responsible for infection control prepare periodic reports called **antibiograms** that record the susceptibility of organisms encountered clinically. These reports are especially useful for detecting the emergence of strains of pathogens resistant to the antibiotics in use at the institution.

CHECK YOUR UNDERSTANDING

In the disk-diffusion test, the zone of inhibition indicating sensitivity around the disk varies with the antibiotic. Why? **20-16**

Clinical Case

Dr. Singh sends her sample of *P. aeruginosa* to the CDC for analysis. The ophthalmologist in the other *P. aeruginosa* case also sends a sample. Using a broth dilution assay, the MIC against these bacteria is 100 µg/ml. The decimal reduction time (DRT) of gentamicin against this bacterium at 4°C was determined to be 4 days and at 23°C, 20 min.

How much time would be required to kill 200 cells at each temperature? (Hint: See Chapter 7.)

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Resistance to Antimicrobial Drugs

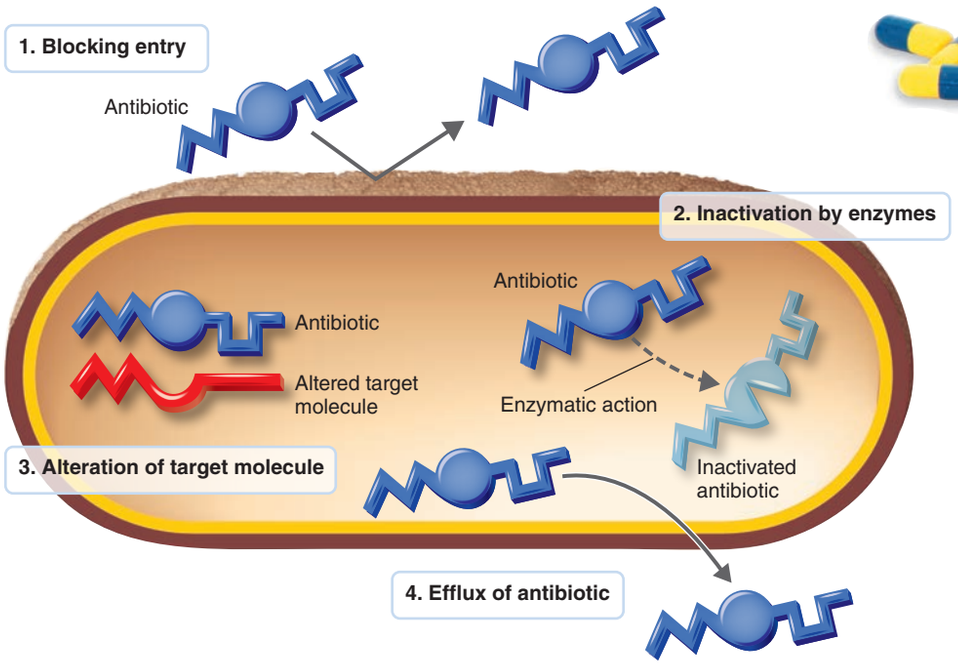
LEARNING OBJECTIVE

20-17 Describe the mechanisms of drug resistance.

One of the triumphs of modern medicine has been the development of antibiotics and other antimicrobials. But the development of resistance to them by the target microbes is an increasing concern. To illustrate this concept, human populations often have a relative resistance to diseases to which they have been exposed for many generations. For example, when Europeans first colonized tropical climes, they proved highly susceptible to diseases they had never been exposed to, although the local populations were relatively resistant. Antibiotics represent, in

FOUNDATION FIGURE 20.20

Bacterial Resistance to Antibiotics





KEY CONCEPTS

- There are only a few mechanisms of microbial resistance to antimicrobial agents: blocking the drug's entry into the cell, inactivation of the drug by enzymes, alteration of the drug's target site, efflux of the drug from the cell, or alteration of the metabolic pathways of the host.
- The mechanisms of bacterial resistance to antibiotics are limited. Knowledge of these mechanisms is critical for understanding the limitations of antibiotic use.

a sense, a disease for bacteria. When first exposed to a new antibiotic, the susceptibility of microbes tends to be high, and their mortality rate is also high; there may be only a handful of survivors from a population of billions. The surviving microbes usually have some genetic characteristic that accounts for their survival, and their progeny are similarly resistant. A term adopted for these bacteria is **persister cells.**

Some genetic differences arise from random mutations. These mutational differences can be spread *horizontally* among bacteria by processes such as conjugation (page 228) or transduction (page 229). Drug resistance is often carried by plasmids or by small segments of DNA called transposons, which can jump from one piece of DNA to another (page 232).

Once acquired, however, the mutation is transmitted by normal reproduction, and the progeny carry the genetic characteristics of the parent microbe. Because of the rapid reproductive rate of bacteria, only a short time elapses before practically the entire population is resistant to the new antibiotic.

Bacteria that are resistant to large numbers of antibiotics are popularly designated as **superbugs.** Although the most publicized of superbugs is MRSA (page 411), superbug status has also been assigned to a range of bacteria, both gram-positive and gram-negative. Faced with infections by such pathogens, medical science has only limited treatment options. MM **Animation** Antibiotic Resistance: Origins of Resistance

Mechanisms of Resistance

There are only a few major mechanisms by which bacteria become resistant to chemotherapeutic agents. See **Figure 20.20**. At least one clinically troublesome bacterium, *Acinetobacter baumanii,* has developed resistance by means of all of the major target sites illustrated in Figure 20.20. MM **Animation** Antibiotic Resistance: Forms of Resistance

Enzymatic Destruction or Inactivation of the Drug

Destruction or inactivation by enzymes mainly affects antibiotics that are natural products, such as the penicillins and cephalosporins. Totally synthetic chemical groups of antibiotics such as the fluoroquinolones are less likely to be affected in this manner, although they can be neutralized in other ways. This may simply reflect the fact that the microbes have had fewer years to adapt to these unfamiliar chemical structures.

The penicillin/cephalosporin antibiotics, and also the carbapenems, share a structure, the β-lactam ring, which is the

target for β-lactamase enzymes that selectively hydrolyze it. Nearly 200 variations of these enzymes are now known, each effective against minor variations in the β-lactam ring structure. When this problem first appeared, the basic penicillin molecule was modified. The first of these penicillinase-resistant drugs was methicillin (see page 558), but resistance to methicillin soon appeared. The best-known of these resistant bacteria is the widely publicized pathogen MRSA, which is resistant to practically all antibiotics, not just methicillin (see the Clinical Focus box on page 411). In a recent year, the CDC ascribed 19,000 deaths to this pathogen. In hospital patients, invasive infections with MRSA can cause as much as 20% mortality. Also, *S. aureus* is not the only bacterium of concern; other important pathogens, such as *Streptococcus pneumoniae,* have also developed resistance to β-lactam antibiotics. Furthermore, MRSA has continued to develop resistance against a succession of new drugs such as vancomycin (the "antibiotic of last resort"), even though this antibiotic has a mode of action against cell wall synthesis that is totally different from that of the penicillins. These highly adaptable bacteria have even developed resistance against antibiotic combinations that include *clavulanic acid,* specifically developed as an inhibitor of β-lactamases (see page 558).

At first, MRSA was almost exclusively a problem in hospitals and similar health-related settings, accounting for about 20% of bloodstream infections there. However, it's now the cause of frequent outbreaks in the general community, is more virulent, and affects otherwise healthy individuals. These strains produce a toxin, a leukocidin, that destroys neutrophils, a primary innate defense against infection. Therefore, the descriptive terminology now differentiates *community-associated MRSA* from *healthcare-associated MRSA*. There is an obvious need for rapid tests to detect MRSA bacteria (generally from nasal swabs) so that infections can be isolated and transmission reduced. The most promising of these are based on PCR technology and yield good results within 1 or 2 hours.

Prevention of Penetration to the Target Site within the Microbe

Gram-negative bacteria are relatively more resistant to antibiotics because of the nature of their cell wall, which restricts absorption of many molecules to movements through openings called porins (see page 81). Some bacterial mutants modify the porin opening so that antibiotics are unable to enter the periplasmic space. Perhaps even more important, when β-lactamases are present in the periplasmic space, the antibiotic that enters is degraded in the periplasmic space, before it can enter the cell.

Alteration of the Drug's Target Site

The synthesis of proteins involves the movement of a ribosome along a strand of messenger RNA, as shown in Figure 20.4. Several antibiotics, especially those of the aminoglycoside, tetracycline, and macrolide groups, utilize a mode of action that inhibits protein synthesis at this site. Minor modifications at this site can neutralize the effects of antibiotics without significantly affecting cellular function.

Interestingly, the main mechanism by which MRSA gained ascendancy over methicillin was not by a new inactivating enzyme, but by modifying the penicillin-binding protein (PBP) on the cell's membrane. β-Lactam antibiotics act by binding with the PBP, which is required to initiate the cross-linking of peptidoglycan and form the cell wall. MRSA strains become resistant because they have an additional, modified, PBP. The antibiotics continue to inhibit the activity of the normal PBPs, preventing their participation in forming the cell wall. But the additional PBP present on the mutants, although it binds weakly with the antibiotic, still allows synthesis of cell walls that is adequate for survival of MRSA strains.

Rapid Efflux (Ejection) of the Antibiotic

Certain proteins in the plasma membranes of gram-negative bacteria act as pumps that expel antibiotics, preventing them from reaching an effective concentration. This mechanism was originally observed with tetracycline antibiotics, but it confers resistance among practically all major classes of antibiotics. Bacteria normally have many such efflux pumps to eliminate toxic substances.

Variations of Mechanisms of Resistance

Variations on these mechanisms also occur. For example, a microbe could become resistant to trimethoprim by synthesizing very large amounts of the enzyme against which the drug is targeted. Conversely, polyene antibiotics can become less effective when resistant organisms produce smaller amounts of the sterols against which the drug is effective. Of particular concern is the possibility that such *resistant mutants* will increasingly replace the susceptible normal populations. **Figure 20.21** shows how rapidly bacterial numbers increase as resistance develops.

Clinical Case

It would take 12 days to kill 200 cells at 4°C and 60 minutes at 23°C. The gentamicin is more effective at the warmer temperature, but the tissues will deteriorate too quickly at this temperature. Hence, the corneas are stored at 4°C to preserve the tissue even though gentamicin is less effective at 4°C.

How might storage of the corneas in gentamicin have contributed to these infections?

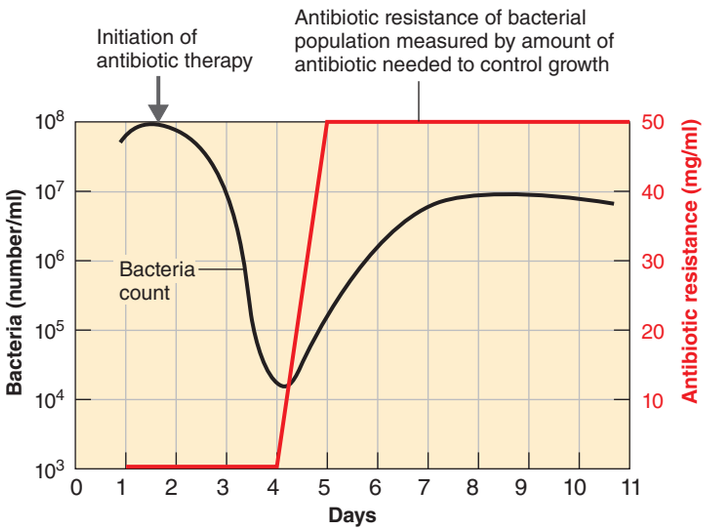


Figure 20.21 The development of an antibiotic-resistant mutant during antibiotic therapy. The patient, suffering from a chronic kidney infection caused by a gram-negative bacterium, was treated with streptomycin. The red line records the antibiotic resistance of the bacterial population. Until about the fourth day, essentially all of the bacterial population is sensitive to the antibiotic. Then mutants in the population that are resistant to streptomycin appear. The bacterial population in the patient rises as these mutants replace the sensitive population.

Q This test used streptomycin and a gram-negative bacterium. What would the lines have looked like if penicillin G had been the antibiotic?

Antibiotic Misuse

Antibiotics have been much misused, nowhere more so than in the less-developed areas of the world. Well-trained personnel are scarce, especially in rural areas, which is perhaps one reason why antibiotics can almost universally be purchased without prescriptions in these countries. A survey in rural Bangladesh, for example, showed that only 8% of antibiotics had been prescribed by a physician. In much of the world, antibiotics are sold to treat headaches and for other inappropriate uses (Figure 20.22). Even when the use of antibiotics is appropriate, dose regimens are usually shorter than needed to eradicate the infection, thereby encouraging the survival of resistant strains of bacteria. Outdated, adulterated (impure), and even counterfeit antibiotics are common.

The developed world is also contributing to the rise of antibiotic resistance. The CDC estimates that in the United States, 30% of the antibiotic prescriptions for ear infections, 100% of the prescriptions for the common cold, and 50% of prescriptions for sore throats were unnecessary or inappropriate to treat the problem pathogen. At least 70% of the antibiotics produced in the United States each year are not used to treat disease but are used in animal feeds to promote growth—a practice that is being discouraged by the CDC and by consumers (see the Clinical Focus box). In 2006, the use of antibiotics as a growth enhancer in animals was banned in European Union countries, and in the United States in 2012, the FDA prohibited the use of cephalosporin-class antibiotics in food-producing animals. In 2013, the FDA also created a voluntary plan for the industry to phase out use of some antibiotics.

Cost and Prevention of Resistance

Antibiotic resistance is costly in many ways beyond those that are apparent in higher rates of disease and mortality. Developing new drugs to replace those that have lost effectiveness is costly. Almost all of these drugs will be more expensive, sometimes priced in a range that makes them difficult to afford even in highly developed countries. In less-developed parts of the world, the costs are simply unaffordable.

There are many strategies that patients and health care workers can adopt to prevent the development of resistance. Even if they feel they have recovered, patients should always finish the full regimen of their antibiotic prescriptions to discourage the survival and proliferation of the antibiotic-resistant microbes. Patients should never use leftover antibiotics to treat new illnesses or use antibiotics that were prescribed to someone else. Health care workers should avoid unnecessary prescriptions and ensure that the choice and dosages of antimicrobials are appropriate to the situation. Prescribing the most specific antibiotic possible, instead of broad-spectrum antimicrobials, also decreases the chances that the antibiotic will inadvertently cause resistance among the patient's normal microbiota.

Strains of bacteria that are resistant to antibiotics are particularly common among hospital workers, where antibiotics are in constant use. When antibiotics are injected, as many are,



Figure 20.22 Antibiotics have been sold without prescriptions for many decades in much of the world.

Q How does this practice lead to development of resistant strains of pathogens?

Antibiotics in Animal Feed Linked to Human Disease

As you read through this box, you will encounter a series of questions that microbiologists ask as they combat antibiotic resistance. Try to answer each question before going on to the next one.

1. Livestock growers use antibiotics in the feed of closely penned animals because the drugs reduce the number of bacterial infections and accelerate the animals' growth. Today, more than half the antibiotics used worldwide are given to farm animals.

   Meat and milk that reach the consumer's table are not heavily laden with antibiotics, so what is the risk of using antibiotics in animal feed?

2. The constant presence of antibiotics in these animals is an example of "survival of the fittest." Antibiotics kill some bacteria, but other bacteria have properties that help them survive.

   How do bacteria acquire resistance genes?

3. Resistance to antimicrobial drugs in bacteria results from mutations. These mutations can be transmitted to other bacteria via horizontal gene transfer (**Figure A**).

   What evidence would show that veterinary use of antibiotics promotes resistance?

4. Vancomycin-resistant *Enterococcus* spp. (VRE) were first isolated in France in 1986 and were found in the United States in 1989. Vancomycin and another glycopeptide, avoparcin, were widely used in animal feed in Europe. In 1997, veterinary use of avoparcin was banned in Europe. After the ban, VRE-positive samples decreased from 100% to 25%, and the human carrier rate dropped from 12% to 3%.

   ***Campylobacter jejuni* is a commensal in the intestines of poultry. What human disease does *C. jejuni* cause?**

5. Annually in the United States, *Campylobacter* causes over 2.5 million foodborne infections. Fluoroquinolone (FQ)-resistant *C. jejuni* in humans emerged in the 1990s (**Figure B**).

   What FQs are used to treat human infections? (*Hint*: See Table 20.3.)

6. The emergence corresponds with the presence of FQ-resistant *C. jejuni* in grocery store–purchased chicken meat. FQ-resistant *C. jejuni* could be selected for in patients who had previously taken an FQ. However, a study of *Campylobacter* isolates from patients between 1997 and 2001 showed that patients infected with FQ-resistant *C. jejuni* had not taken an FQ prior to their illness and had not traveled out of the United States.

   Suggest a way to decrease emergence of FQ resistance.

7. The use of FQ in chicken feed was banned in 2005, in hope of reducing FQ resistance. A variety of approaches may be necessary to reduce the possibility of illness: (1) prevent colonization in the animals at the farm, (2) reduce fecal contamination of meat during processing at the slaughterhouse, and (3) use proper storage and cooking methods.

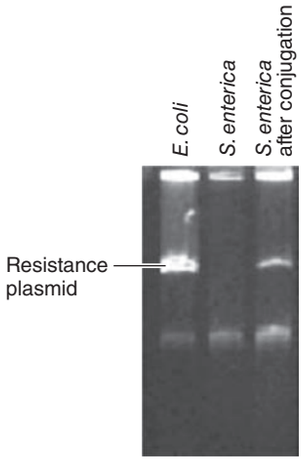


Figure A **Cephalosporin resistance in *E. coli* transferred by conjugation to *Salmonella enterica* in the intestinal tracts of turkeys.**

Data sources: CDC and National Microbial Resistance Monitoring System.

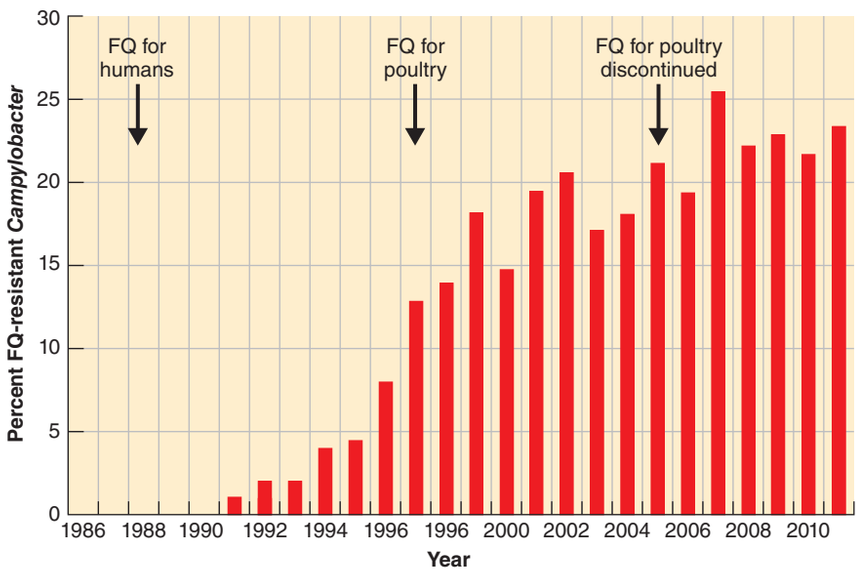


Figure B **Fluoroquinolone-resistant *Campylobacter jejuni* in the United States, 1986–2011.**

Clinical Case

Gentamicin is used in commercial storage medium for corneas because it has been reported to be more effective than penicillin or cephalothin in reducing the colony counts of staphylococci and gram-negative rods in a buffered storage medium. Adding gentamicin is intended to preserve the medium before use, not to sterilize corneal tissue. Storage in an antibiotic could select for antibiotic-resistant bacteria.

What antimicrobial drug would work best to treat *P. aeruginosa*?

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the syringe must first be held vertically and cleared of air bubbles, a practice that causes aerosols of the antibiotic solution to form. When the nurse or physician inhales these aerosols, the microbial inhabitants of the nostrils are exposed to the drug. Inserting the needle into sterile cotton to expel air bubbles can prevent aerosols from forming. Many hospitals have special monitoring committees to review the use of antibiotics for effectiveness and cost.

CHECK YOUR UNDERSTANDING

- What is the most common mechanism that a bacterium uses to resist the effects of penicillin? **20-17**

Antibiotic Safety

In our discussions of antibiotics, we have occasionally mentioned side effects. These may be potentially serious, such as liver or kidney damage or hearing impairment. Administering almost any drug involves assessing risks against benefits; this is called the *therapeutic index*. Sometimes, the use of another drug can cause toxic effects that do not occur when the drug is taken alone. One drug may also neutralize the intended effects of the other. For example, a few antibiotics have been reported to neutralize the effectiveness of contraceptive pills. Also, some individuals may have hypersensitivity reactions, for example, to penicillins (see the Clinical Focus box on page 527).

A pregnant woman should take only those antibiotics that are classified by the U.S. Food and Drug Administration as presenting no evidence of risk to the fetus.

Effects of Combinations of Drugs

LEARNING OBJECTIVE

20-18 Compare and contrast synergism and antagonism.

The chemotherapeutic effect of two drugs given simultaneously is sometimes greater than the effect of either given alone

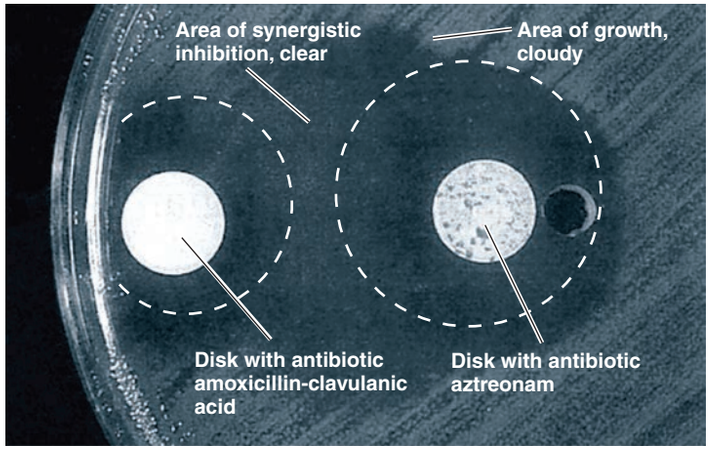


Figure 20.23 An example of synergism between two different antibiotics. The photograph shows the surface of a Petri plate seeded with bacteria. The paper disk at the left contains the antibiotic amoxicillin plus clavulanic acid. The disk on the right contains the antibiotic aztreonam. The dashed circles drawn over the photo show the clear areas surrounding each disk where bacterial growth would have been inhibited if there had been no synergy. The additional clear area between these two areas and outside the drawn circles illustrates inhibition of bacterial growth through the effects of synergy.

Q What would the plate look like if the two antibiotics had been antagonistic?

(Figure 20.23). This phenomenon, called **synergism,** was introduced earlier. For example, in the treatment of bacterial endocarditis, penicillin and streptomycin are much more effective when taken together than when either drug is taken alone. Damage to bacterial cell walls by penicillin makes it easier for streptomycin to enter.

Other combinations of drugs can show **antagonism.** For example, the simultaneous use of penicillin and tetracycline is often less effective than when either drug is used alone. By stopping the growth of the bacteria, the bacteriostatic drug tetracycline interferes with the action of penicillin, which requires bacterial growth.

CHECK YOUR UNDERSTANDING

- Tetracycline sometimes interferes with the activity of penicillin. How? **20-18**

Future of Chemotherapeutic Agents

LEARNING OBJECTIVE

20-19 Name three areas of research on new chemotherapeutic agents.

As pathogens develop resistance to current chemotherapeutic agents, the need for new ones becomes more pressing. However, developing new antimicrobial agents is not especially

profitable. Like vaccines, antimicrobials are used only on infrequent occasions for limited periods of time. Pharmaceutical companies are understandably more interested in developing drugs that treat chronic conditions, such as high blood pressure or diabetes, for which a patient requires years of regular medication. This has led to something of a "perfect storm"—increasing drug resistance combined with a decline in the development of new antibiotics. There is genuine concern that we may be approaching a post-antibiotic time when infections of minor cuts or scratches might again cause deaths.

Existing antibiotics continue to encounter problems with resistance in large part because their developers have relied on a limited range of targets (see Figure 20.2). A truly new approach to controlling pathogens is to target their virulence factors rather than the microbe producing them. For example, instead of targeting the cholera bacillus, a drug might target the cholera toxin, neutralizing or destroying it. Another potential target is to sequester iron, which pathogens need for growth. A drug that sequesters iron would therefore limit proliferation of the pathogens.

The FDA requires that antibiotics be tested against exponentially growing pathogens. This has led to a near-absence of drugs to combat dormant cells, especially the persisters (page 570). Most drugs fail when tested against such cells. Another basic problem awaiting a solution is a lack of drugs that treat gram-negative infections. The cell wall of gram-negative bacteria makes them inherently resistant to most antibiotics. In fact, the antibiotics developed over the past few decades have worked only against gram-positive species. Also, over 99% of bacterial species found in nature are incapable of being grown on conventional laboratory media. Attempting to reproduce the cellular environment in the lab to grow and test antibiotic sensitivity of noncultivatable bacteria is complicated and expensive. Multidrug resistance of the bacteria comprising biofilms is another unsolved problem. Finally, drug misuse based on unregulated distribution of antimicrobial drugs speeds up antibiotic resistance in many parts of the world.

New, exotic ecological niches, such as deep-sea sediments, will need to be explored. It's thought that organisms in extreme environments might have developed novel mechanisms to deal with these conditions. Microorganisms are not the only organisms that produce antimicrobial substances. Many birds, amphibians, plants, and mammals often produce *antimicrobial peptides.* In fact, such peptides are part of the defense systems of most forms of life, and literally hundreds of such peptides have been identified. Amphibian skin glands are a rich source of antimicrobial peptides that attack bacterial membranes. The best-known of these are the *magainins* (from the Hebrew for shield). It's especially interesting that this antimicrobial has existed for an indefinite time without significant development of resistance. Another antimicrobial substance, a steroid named *squalamine,* has been isolated from sharks.

The most promising new avenue of research to develop new antibiotics will probably be based on knowledge of the basic genetic structure of microbes—knowledge that may help us identify new targets for antimicrobials. For example, this is the approach that has led to the development of protease inhibitors for HIV. The development of fully synthetic molecules (such as the quinolones and the oxazolidinones) will be of increasing importance.

Perhaps there will be renewed interest in *phage therapy.* At one time it was observed that bacteriophages, viruses that attack bacteria, were capable of killing specific pathogenic bacteria. Early experiments in phage therapy were not very successful, but Russian scientists, in particular, have continued to experiment with phage therapy. Environmentally, the soil is full of bacteriophages, and it's said that every couple of days they kill about half the bacteria on Earth. Similarly, many bacteria produce antimicrobial peptides called *bacteriocins* (see Chapter 14, page 391). Research has shown some of these exhibit a broad spectrum of activity whereas others have a narrow spectrum. The mechanisms of action differ from those of most antibiotics. Some bacteriocins affect the cell membrane, and others affect protein production. The oral toxicity of bacteriocins is very low.

Serendipity, or accidental discovery, is always a consideration. For example, it's worth mentioning that the first quinolone, nalidixic acid, was discovered as an intermediate in the synthesis of an antimalarial drug, chloroquine, and that the oxazolidinones were originally developed to treat plant diseases.

Finally, there is a special need for new antiviral drugs as well as antifungal and antiparasitic drugs effective against helminths and protozoans, because our arsenal in these categories is very limited.

CHECK YOUR UNDERSTANDING

What are defensins? (*Hint:* See Chapter 16.) **20–19**

Clinical Case Resolved

Dr. Singh prescribes doripenem for her patient. Doripenem is a carbapenem, which has an extremely broad spectrum of activity and is especially effective against *P. aeruginosa.* The patient recovers from her infection and has no further complications from her surgery.

Study Outline

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Introduction (p. 548)

1. An antimicrobial drug is a chemical substance that destroys pathogenic microorganisms with minimal damage to host tissues.
2. Chemotherapeutic agents include chemicals that combat disease in the body.

The History of Chemotherapy (pp. 549–550)

1. Paul Ehrlich developed the concept of chemotherapy to treat microbial diseases; he predicted the development of chemotherapeutic agents, which would kill pathogens without harming the host.
2. Sulfa drugs came into prominence in the 1930s.
3. Alexander Fleming discovered the first antibiotic, penicillin, in 1928; its first clinical trials were done in 1940.

The Spectrum of Antimicrobial Activity (pp. 550–551)

1. Antibacterial drugs affect many targets in a prokaryotic cell.
2. Fungal, protozoan, and helminthic infections are more difficult to treat because these organisms have eukaryotic cells.
3. Narrow-spectrum drugs affect only a select group of microbes—gram-positive cells, for example; broad-spectrum drugs affect a more diverse range of microbes.
4. Small, hydrophilic drugs can affect gram-negative cells.
5. Antimicrobial agents should not cause excessive harm to normal microbiota.
6. Superinfections occur when a pathogen develops resistance to the drug being used or when normally resistant microbiota multiply excessively.

The Action of Antimicrobial Drugs (pp. 551–553)

1. Antimicrobials generally act either by directly killing microorganisms (bactericidal) or by inhibiting their growth (bacteriostatic).
2. Some agents, such as penicillin, inhibit cell wall synthesis in bacteria.
3. Other agents, such as chloramphenicol, tetracyclines, and streptomycin, inhibit protein synthesis by acting on 70S ribosomes.
4. Antifungal agents target plasma membranes.
5. Some agents inhibit nucleic acid synthesis.
6. Agents such as sulfanilamide act as antimetabolites by competitively inhibiting enzyme activity.

Common Antimicrobial Drugs (pp. 554–567)

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis (pp. 554–559)

1. All penicillins contain a β-lactam ring.
2. Natural penicillins produced by *Penicillium* are effective against gram-positive cocci and spirochetes.
3. Penicillinases (β-lactamases) are bacterial enzymes that destroy natural penicillins.
4. Semisynthetic penicillins are made in the laboratory by adding different side chains onto the β-lactam ring made by the fungus.
5. Semisynthetic penicillins are resistant to penicillinases and have a broader spectrum of activity than natural penicillins.
6. Carbapenems are broad-spectrum antibiotics that inhibit cell wall synthesis.
7. The monobactam aztreonam affects only gram-negative bacteria.
8. Cephalosporins inhibit cell wall synthesis and are used against penicillin-resistant strains.
9. Polypeptides such as bacitracin inhibit cell wall synthesis primarily in gram-positive bacteria.
10. Vancomycin inhibits cell wall synthesis and may be used to kill penicillinase-producing staphylococci.

Antimycobacterial Antibiotics (pp. 559–560)

11. Isoniazid (INH) and ethambutol inhibit cell wall synthesis in mycobacteria.

Inhibitors of Protein Synthesis (pp. 560–562)

12. Chloramphenicol, aminoglycosides, tetracyclines, glycylcyclines, macrolides, streptogramins, oxazolidinones, and pleuromutilins inhibit protein synthesis at 70S ribosomes.

Injury to the Plasma Membrane (p. 562)

13. Lipopeptides polymyxin B and bacitracin cause damage to plasma membranes.

Nucleic Acid Synthesis Inhibitors (pp. 562–563)

14. Rifamycin inhibits mRNA synthesis; it's used to treat tuberculosis.
15. Quinolones and fluoroquinolones inhibit DNA gyrase for treating urinary tract infections.

Competitive Inhibition of Essential Metabolites (p. 563)

16. Sulfonamides competitively inhibit folic acid synthesis.
17. TMP-SMZ competitively inhibits dihydrofolic acid synthesis.

Antifungal Drugs (pp. 564–565)

18. Polyenes, such as nystatin and amphotericin B, combine with plasma membrane sterols and are fungicidal.
19. Azoles and allylamines interfere with sterol synthesis and are used to treat cutaneous and systemic mycoses.
20. Echinocandins interfere with fungal cell wall synthesis.
21. The antifungal agent flucytosine is an antimetabolite of cytosine.
22. Griseofulvin interferes with eukaryotic cell division and is used primarily to treat skin infections caused by fungi.

Antiviral Drugs (pp. 565–567)

23. Entry inhibitors and fusion inhibitors bind to HIV attachment and receptor sites.
24. Nucleoside and nucleotide analogs, such as acyclovir and zidovudine, inhibit DNA or RNA synthesis.
25. Inhibitors of viral enzymes are used to treat influenza and HIV infection.
26. Alpha interferons inhibit the spread of viruses to new cells.

Antiprotozoan and Antihelminthic Drugs (p. 567)

27. Chloroquine, artemisinin, quinacrine, diiodohydroxyquin, pentamidine, and metronidazole are used to treat protozoan infections.
28. Antihelminthic drugs include mebendazole, praziquantel, and ivermectin.

Tests to Guide Chemotherapy (pp. 567–569)

1. Tests are used to determine which chemotherapeutic agent is most likely to combat a specific pathogen.
2. These tests are used when susceptibility cannot be predicted or when drug resistance arises.

The Diffusion Methods (p. 568)

3. In the disk-diffusion test, also known as the Kirby-Bauer test, a bacterial culture is inoculated on an agar medium, and filter paper disks impregnated with chemotherapeutic agents are overlaid on the culture.
4. After incubation, the diameter of the zone of inhibition is used to determine whether the organism is sensitive, intermediate, or resistant to the drug.
5. MIC is the lowest concentration of drug capable of preventing microbial growth; MIC can be estimated using the E test.

Broth Dilution Tests (pp. 568–569)

6. In a broth dilution test, the microorganism is grown in liquid media containing different concentrations of a chemotherapeutic agent.
7. The lowest concentration of a chemotherapeutic agent that kills bacteria is called the minimum bactericidal concentration (MBC).

Resistance to Antimicrobial Drugs (pp. 569–574)

1. Many bacterial diseases, previously treatable with antibiotics, have become resistant to antibiotics.
2. Superbugs are bacteria that are resistant to several antibiotics.
3. Drug resistance factors are transferred horizontally between bacteria.
4. Resistance may be due to enzymatic destruction of a drug, prevention of penetration of the drug to its target site, cellular or metabolic changes at target sites, altering the target site, or rapid efflux of the antibiotic.
5. The discriminating use of drugs in appropriate concentrations and dosages can minimize resistance.

Antibiotic Safety (p. 574)

1. The risk (e.g., side effects) versus the benefit (e.g., curing an infection) must be evaluated before antibiotics are used.

Effects of Combinations of Drugs (p. 574)

1. Some combinations of drugs are synergistic; they are more effective when taken together.
2. Some combinations of drugs are antagonistic; when taken together, both drugs become less effective than when taken alone.

Future of Chemotherapeutic Agents (pp. 574–575)

1. New agents include antimicrobial peptides, bacteriocins, and bacteriophages.
2. Virulence factors rather than cell growth factors may provide new targets.

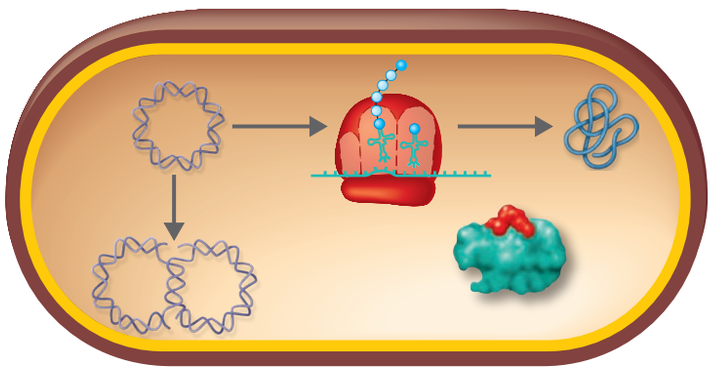
Study Questions

For answers to the Knowledge & Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. DRAW IT Show where the following antibiotics work: ciprofloxacin, tetracycline, streptomycin, vancomycin, polymyxin B, sulfanilamide, rifampin, erythromycin.



2. List and explain five criteria used to identify an effective antimicrobial agent.
3. What similar problems are encountered with antiviral, antifungal, antiprotozoan, and antihelminthic drugs?
4. Define *drug resistance.* How is it produced? What measures can be taken to minimize drug resistance?
5. List the advantages of using two chemotherapeutic agents simultaneously to treat a disease. What problem can be encountered using two drugs?
6. Why does a cell die from the following antimicrobial actions?
   a. Colistimethate binds to phospholipids.
   b. Kanamycin binds to 70S ribosomes.
7. How does each of the following inhibit translation?
   a. chloroamphenicol
   b. erythromycin
   c. tetracycline
   d. streptomycin
   e. oxazolidinone
   f. streptogramin
8. Dideoxyinosine (ddI) is an antimetabolite of guanine. The –OH is missing from carbon 3′ in ddI. How does ddI inhibit DNA synthesis?
9. Compare the method of action of the following pairs:
   a. penicillin and echinocandin
   b. imidazole and polymyxin B
10. NAME IT This microorganism is not susceptible to antibiotics or neuromuscular blocks, but it's susceptible to protease inhibitors.

Multiple Choice

1. Which of the following pairs is *mismatched*?
   a. antihelminthic—inhibition of oxidative phosphorylation
   b. antihelminthic—inhibition of cell wall synthesis
   c. antifungal—injury to plasma membrane
   d. antifungal—inhibition of mitosis
   e. antiviral—inhibition of DNA synthesis
2. All of the following are modes of action of antiviral drugs *except*
   a. inhibition of protein synthesis at 70S ribosomes.
   b. inhibition of DNA synthesis.
   c. inhibition of RNA synthesis.
   d. inhibition of uncoating.
   e. All of the above are modes of action of antiviral drugs.
3. Which of the following modes of action would *not* be fungicidal?
   a. inhibition of peptidoglycan synthesis
   b. inhibition of mitosis
   c. injury to the plasma membrane
   d. inhibition of nucleic acid synthesis
   e. All of the above are fungicidal modes of action.
4. An antimicrobial agent should meet all of the following criteria *except*
   a. selective toxicity.
   b. the production of hypersensitivities.
   c. a narrow spectrum of activity.
   d. no production of drug resistance.
   e. All of the above are necessary criteria for an antimicrobial.
5. The most selective antimicrobial activity would be exhibited by a drug that
   a. inhibits cell wall synthesis.
   b. inhibits protein synthesis.
   c. injures the plasma membrane.
   d. inhibits nucleic acid synthesis.
   e. all of the above
6. Antibiotics that inhibit translation have side effects
   a. because all cells have proteins.
   b. only in the few cells that make proteins.
   c. because eukaryotic cells have 80S ribosomes.
   d. at the 70S ribosomes in eukaryotic cells.
   e. None of the above is correct.
7. Which of the following will *not* affect eukaryotic cells?
   a. inhibition of the mitotic spindle
   b. binding with sterols
   c. binding to 80S ribosomes
   d. binding to DNA
   e. All of the above will affect them.
8. Cell membrane damage causes death because
   a. the cell undergoes osmotic lysis.
   b. cell contents leak out.
   c. the cell plasmolyzes.
   d. the cell lacks a wall.
   e. None of the above is correct.
9. A drug that intercalates into DNA has the following effects. Which one leads to the others?
   a. It disrupts transcription.
   b. It disrupts translation.
   c. It interferes with DNA replication.
   d. It causes mutations.
   e. It alters proteins.
10. Chloramphenicol binds to the 50S portion of a ribosome, which will interfere with
    a. transcription in prokaryotic cells.
    b. transcription in eukaryotic cells.
    c. translation in prokaryotic cells.
    d. translation in eukaryotic cells.
    e. DNA synthesis.

Analysis

1. Which of the following can affect human cells? Explain why.
   a. penicillin
   b. indinavir
   c. erythromycin
   d. polymyxin
2. Why is idoxuridine effective if host cells also contain DNA?
3. Some bacteria become resistant to tetracycline because they don't make porins. Why can a porin-deficient mutant be detected by its inability to grow on a medium containing a single carbon source such as succinic acid?
4. The following data were obtained from a disk-diffusion test.

Antibiotic	Zone of Inhibition
A	15 mm
B	0 mm
C	7 mm
D	15 mm

   a. Which antibiotic was most effective against the bacteria being tested?
   b. Which antibiotic would you recommend for treating a disease caused by this bacterium?
   c. Was antibiotic A bactericidal or bacteriostatic? How can you tell?
5. Why do you suppose *Streptomyces griseus* produces an enzyme that inactivates streptomycin? Why is this enzyme produced early in metabolism?
6. The following results were obtained from a broth dilution test for microbial susceptibility.

Antibiotic Concentration	Growth	Growth in Subculture
200 µg/ml	–	–
100 µg/ml	–	+
50 µg/ml	+	+
25 µg/ml	+	+

   a. The MIC of this antibiotic is _____.
   b. The MBC of this antibiotic is _____.

Clinical Applications and Evaluation

1. Vancomycin-resistant *Enterococcus faecalis* was isolated from a foot infection of a 40-year-old man. The patient had a chronic diabetes-related foot ulcer and underwent amputation of a gangrenous toe. He subsequently developed methicillin-resistant *Staphylococcus aureus* bacteremia. The infection was treated with vancomycin. One week later, he developed a vancomycin-resistant *S. aureus* (VRSA) infection. This is the first case of VRSA in the United States. What is the most likely source of the VRSA?
2. A patient with a urinary bladder infection took nalidixic acid, but her condition did not improve. Explain why her infection disappeared when she switched to a sulfonamide.
3. A patient with streptococcal sore throat takes penicillin for 2 days of a prescribed 10-day regimen. Because he feels better, he then saves the remaining penicillin for some other time. After 3 more days, he suffers a relapse of the sore throat. Discuss the probable cause of the relapse.



In the Clinic

As the intake nurse at the clinic, you see a 5-year-old boy with a rash on his hands and feet. His mother explains that he has had the rash for the past few days. There are no other symptoms. All other family members are well. The boy attends kindergarten and day care. His temperature is 37.6°C. You first need to assess the rash. You note that it is maculopapular with a few vesicles. You've seen a few of these rashes this month. **Is this an exanthem or enanthem? What is the disease?**

Hint: See the discussion about viral diseases of the skin on pages 590–595.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

21

Microbial Diseases of the Skin and Eyes

The skin, which covers and protects the body, is the body's first line of defense against pathogens. As a physical barrier, it is almost impossible for pathogens to penetrate the intact skin. Microbes can, however, enter through skin breaks that are not readily apparent, and the larval forms of a few parasites can penetrate intact skin.

The skin is an inhospitable place for most microorganisms because the secretions of the skin are acidic and most of the skin contains little moisture. Some parts of the body, though, such as the armpit and the area between the legs, have enough moisture to support relatively large bacterial populations. Drier regions, such as the scalp, support rather small numbers of microorganisms. A few microbes that colonize skin can cause disease. One such bacterium is *Staphylococcus aureus*, shown in the photograph. The Clinical Case in this chapter describes how an opportunistic pathogen can cause a skin infection.

Color enhanced scanning electron micrograph (SEM) of *Staphylococcus aureus*, bacteria that commonly live on the skin or in the nose of healthy people.

Structure and Function of the Skin

LEARNING OBJECTIVE

21-1 Describe the structure of the skin and mucous membranes and the ways pathogens can invade the skin.

The skin of an average adult occupies a surface area of about 1.9 m^2 and varies in thickness from 0.05 to 3.0 mm. Skin consists of two principal parts, the epidermis and the dermis (Figure 21.1). The **epidermis** is the thin outer portion, composed of several layers of epithelial cells. The outermost layer of the epidermis, the *stratum corneum,* consists of many rows of dead cells that contain a waterproofing protein called **keratin.** The epidermis, when unbroken, is an effective physical barrier against microorganisms.

The **dermis** is the inner, relatively thick portion of skin, composed mainly of connective tissue. The hair follicles, sweat gland ducts, and oil gland ducts in the dermis provide passageways through which microorganisms can enter the skin and penetrate deeper tissues.

Perspiration provides moisture and some nutrients for microbial growth. However, it contains salt, which inhibits many microorganisms; the enzyme lysozyme, which is capable of breaking down the cell walls of certain bacteria; and antimicrobial peptides.

Sebum, secreted by oil glands, is a mixture of lipids (unsaturated fatty acids), proteins, and salts that prevents skin and hair from drying out. Although the fatty acids inhibit the growth of certain pathogens, sebum, like perspiration, is also nutritive for many microorganisms.

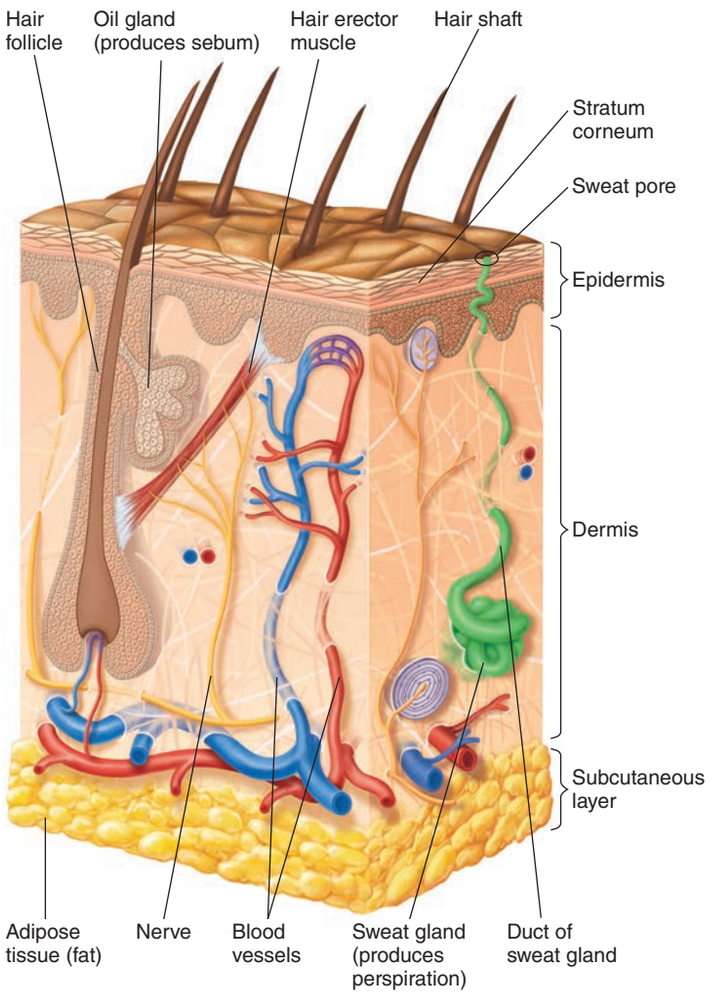


Figure 21.1 The structure of human skin. Notice the passageways between the hair follicle and hair shaft, through which microbes can penetrate the deeper tissues. They can also enter the skin through sweat pores.

Q What do you perceive from this illustration to be the weak points that would allow microbes to reach the underlying tissue by penetrating intact skin?

Mucous Membranes

In the linings of body cavities that open to the exterior, such as those associated with the gastrointestinal, respiratory, urinary, and genital tracts, the outer protective barrier differs from the skin. It consists of sheets of tightly packed *epithelial cells.* These cells are attached at their bases to a layer of extracellular material called the *basement membrane.* Many of these cells secrete mucus—hence the name **mucous membrane,** or **mucosa.** Other mucosal cells have cilia; and, in the respiratory system, the mucous layer traps particles, including microorganisms, which the cilia sweep upward out of the body (see Figure 16.3, page 444). Mucous membranes are often acidic, which tends to limit their microbial populations. Also, the membranes of the eyes are mechanically washed by tears, and the lysozyme in tears destroys the cell walls of certain bacteria. Mucous membranes are often folded to maximize surface area; the total surface area in an average human is about 400 m^2, much more than the surface area of the skin.

CHECK YOUR UNDERSTANDING

✓ Moisture in perspiration encourages microbial growth. What perspiration factors discourage growth? **21-1**

Normal Microbiota of the Skin

LEARNING OBJECTIVE

21-2 Provide examples of normal skin microbiota, and state the general locations and ecological roles of its members.

Although the skin is generally inhospitable to most microorganisms, certain microbes are part of the normal microbiota. On superficial skin surfaces, certain aerobic bacteria produce fatty acids from sebum. These acids inhibit many microbes and allow better-adapted bacteria to flourish.

Microorganisms that find the skin a satisfactory environment are resistant to drying and to relatively high salt concentrations. The skin's normal microbiota contain relatively large numbers of gram-positive cocci, such as staphylococci and micrococci. These bacteria tend to be resistant to dry environments, and to the high osmotic pressures found in concentrated salt or sugar solutions.

Scanning electron micrographs show that bacteria on the skin are often grouped into small clumps. Vigorous washing can reduce their numbers but will not eliminate them. Microorganisms remaining in hair follicles and sweat glands after washing will soon reestablish the normal populations. Areas of the body with more moisture, such as the armpits and between the legs, have higher populations of microbes. These metabolize secretions from the sweat glands and are the main contributors to body odor.

Also part of the skin's normal microbiota are gram-positive pleomorphic rods called *diphtheroids.* Some diphtheroids, such as *Propionibacterium acnes,* are typically anaerobic and inhabit hair follicles. Their growth is supported by secretions from the oil glands (sebum), which, as we will see, makes them a factor in acne. These bacteria produce propionic acid, which helps maintain the low pH of skin, generally between 3 and 5. Other diphtheroids, such as *Corynebacterium xerosis* (zer-Ō-sis), are aerobic and occupy the skin surface.

A few gram-negative bacteria, especially *Acinetobacter,* colonize the skin. A yeast, *Malassezia furfur,* is capable of growing on oily skin secretions and is thought to be responsible for the scaling skin condition known as *dandruff.* Shampoos for treating dandruff contain the antibiotic ketoconazole or zinc pyrithione or selenium sulfide. All are active against this yeast.

CHECK YOUR UNDERSTANDING

- Are skin bacteria more likely to be gram-positive or gram-negative? **21-2**

Microbial Diseases of the Skin

LEARNING OBJECTIVES

21-3 Differentiate staphylococci from streptococci, and name several skin infections caused by each.

21-4 List the causative agent, mode of transmission, and clinical symptoms of *Pseudomonas* dermatitis, otitis externa, acne, and Buruli ulcer.

21-5 List causative agents, modes of transmission, and symptoms of warts, smallpox, monkeypox, chickenpox, shingles, cold sores, measles, rubella, fifth disease, hand-foot-and-mouth disease, and roseola.

21-6 Differentiate cutaneous from subcutaneous mycoses, and provide an example of each.

21-7 List the causative agent and predisposing factors for candidiasis.

21-8 List the causative agent, mode of transmission, clinical symptoms, and treatment for scabies and pediculosis.

Rashes and lesions on the skin do not necessarily indicate an infection of the skin; in fact, many skin lesions are actually caused by systemic diseases affecting internal organs. Preliminary diagnosis is often based on the appearance of the rash, so it is important to understand the terms that describe rashes. For example, small, fluid-filled lesions are **vesicles** (Figure 21.2a). Vesicles larger than about 1 cm in diameter are termed **bullae** (Figure 21.2b). Flat, reddened lesions are known as **macules** (Figure 21.2c). Raised lesions are called **papules** or, when they contain pus, **pustules** (Figure 21.2d). A skin rash that arises from disease conditions is called an **exanthem;** on mucous membranes, such as the interior of the mouth, such a rash is called an **enanthem.**

Bacterial Diseases of the Skin

Two genera of bacteria, *Staphylococcus* and *Streptococcus,* are frequent causes of skin-related diseases and merit special discussion. We will also discuss these bacteria in subsequent chapters in relation to other organs and conditions. Superficial staphylococcal and streptococcal infections of the skin are very common. Both genera also may produce invasive enzymes and damaging toxins.

Staphylococcal Skin Infections

Staphylococci are spherical gram-positive bacteria that form irregular clusters like grapes (see Figure 4.1d, page 74, and Figure 11.22, page 309). For almost all clinical purposes, these bacteria can be divided into those that produce **coagulase,** an enzyme that coagulates (clots) fibrin in blood, and those that do not.

Coagulase-negative strains, such as *Staphylococcus epidermidis,* are very common on the skin, where they may represent 90% of the normal microbiota. They are generally pathogenic only when the skin barrier is broken or is invaded by medical procedures, such as the insertion and removal of catheters into veins. On the surface of the catheter (Figure 21.3), the bacteria are surrounded by a slime layer of capsular material that protects them from desiccation and disinfectants (see discussions of biofilms on pages 54 and 156). This is a primary factor in their importance as a healthcare-associated pathogen.

Clinical Case: Swimming Lessons

Molly Seidel, a pediatric nurse practitioner, is examining 9-year-old Donald and his 6-year-old sister, Sharon. According to their mother, both children developed rashes around dinner time the evening before. The rashes are similarly distributed over the children's front torsos and thighs. A cloudy fluid discharges when the children scratch the itchy, raised pimples. Molly has already seen several cases of skin rashes in children today. She has diagnosed two children with chickenpox, and she has prescribed penicillin for another child with staphylococcal folliculitis.

What should Molly do next? Read on to find out.

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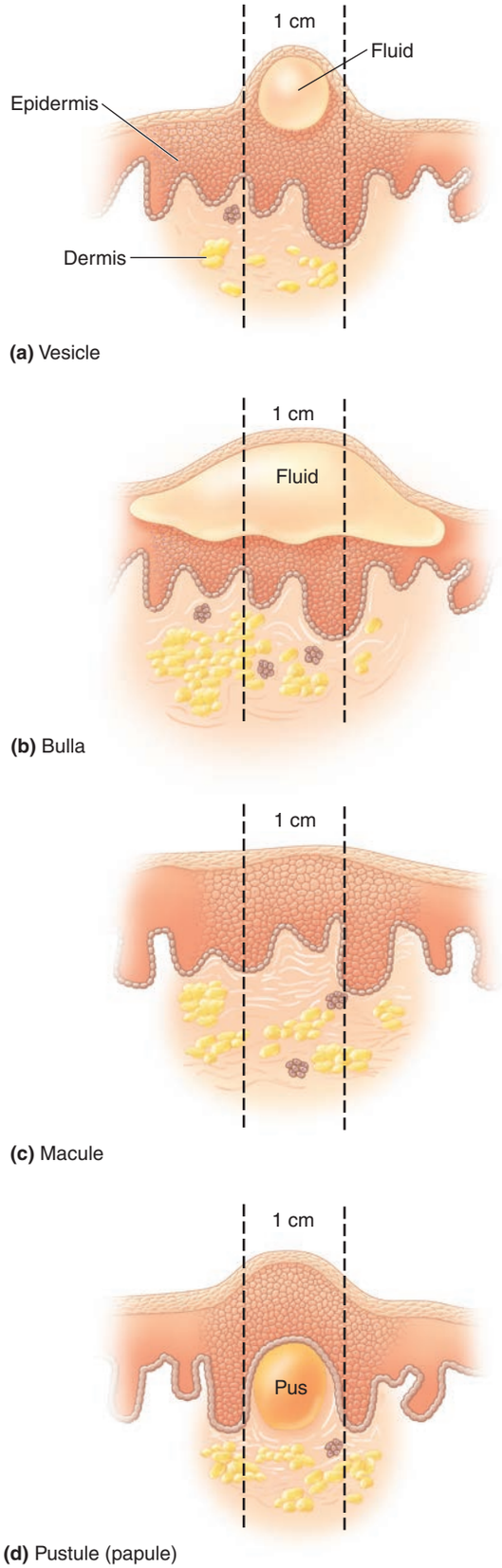
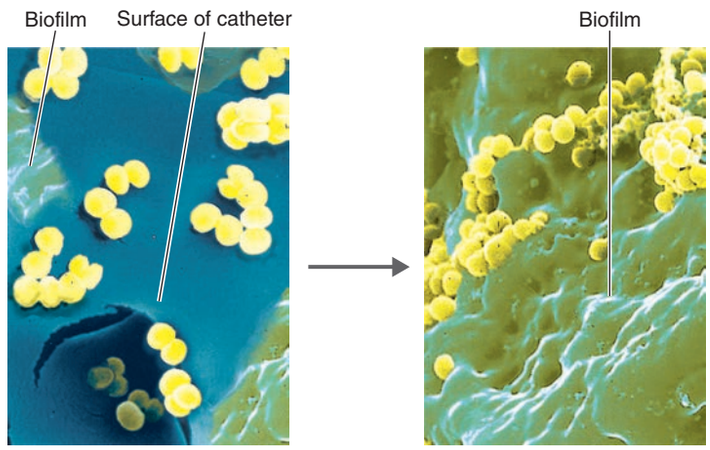


Figure 21.2 Skin lesions. **(a)** Vesicles are small, fluid-filled lesions. **(b)** Bullae are larger fluid-filled lesions. **(c)** Macules are flat lesions that are often reddish. **(d)** Papules are raised lesions; when they contain pus, as shown here, they are called pustules.

Q Are these skin lesions exanthems or enanthems?

S. aureus is the most pathogenic of the staphylococci (also see the discussion of MRSA in Chapter 20). It is a permanent resident of the nasal passages of 20% of the population, and an additional 60% carry it there occasionally. It can survive for months on surfaces. Typically, it forms golden-yellow colonies. This pigmentation protects against the antimicrobial effects of sunlight; mutants without it are also more susceptible to killing by neutrophils. Compared to its more innocuous relative *S. epidermidis, S. aureus* has about 300,000 more base pairs in its genome—much of it devoted to an impressive array of virulence factors and means of evading host defenses. Almost all pathogenic strains of *S. aureus* are coagulase-positive. This is significant because there is a high correlation between the bacterium's ability to form coagulase and its production of damaging toxins, several of which facilitate the spread of the organism in tissue, damage tissue, or are lethal to host defenses. In addition, some strains can cause life-threatening sepsis (Chapter 23, page 639), and others produce *enterotoxins* that affect the gastrointestinal tract (see Chapter 25, pages 713–714).



(a) Catheter surface with adhering bacteria. Biofilm, light green, is beginning to appear.

(b) Most of the bacteria producing the slime are not visible under the biofilm.

Figure 21.3 Coagulase-negative staphylococci. These slime-producing bacteria are the most common causative agents of infection by indwelling devices. They adhere to surfaces such as the plastic catheter in the photos. Once they have adhered to the surface **(a),** they begin to divide. Eventually **(b),** the entire surface is coated with a biofilm containing the organisms.

Q What is the most likely source of the bacteria that grew on the catheter?



Figure 21.4 Lesions of impetigo. This disease is characterized by isolated pustules that become crusted.

What bacteria most often cause impetigo?

Once *S. aureus* infects the skin, it stimulates a vigorous inflammatory response, and macrophages and neutrophils are attracted to the site of infection. However, the bacteria have several ways to evade these host defenses. Most strains secrete a protein that blocks chemotaxis of neutrophils to the infection site, and if the bacterium does encounter phagocytic cells, it often produces toxins that kills them. It is resistant to opsonization (see page 450), but, failing this, it can survive well within the phagosome. Other proteins it secretes neutralize the antimicrobial peptide defensins on skin, and its cell wall is lysozyme resistant (see page 83). It sometimes responds to the immune system as a superantigen (see page 427) but often is able to evade the adaptive immune system entirely. All humans possess antibodies against *S. aureus,* but they do not effectively prevent repeated infections. Antibiotic-resistant strains of *S. aureus* have emerged in hospitals and in the community. (See the Clinical Focus box on page 411, as well as the MRSA discussion on page 558.)

Because this organism is so commonly present in human nasal passages, it is often transported from there to the skin, where it can enter the body through natural openings such as the hair follicle (see Figure 21.1). Such infections, called **folliculitis,** often occur as pimples. The infected follicle of an eyelash is called a **sty.** A more serious hair follicle infection is the **furuncle (boil),** which is a type of **abscess,** a localized region of pus surrounded by inflamed tissue. Antibiotics do not penetrate well into abscesses, and the infection is therefore difficult to treat. Draining pus from the abscess is frequently a preliminary step to successful treatment.

When the body fails to wall off a furuncle, neighboring tissue can be progressively invaded. The extensive damage is called a **carbuncle,** a hard, round deep inflammation of tissue under the skin. At this stage of infection, the patient usually exhibits the symptoms of generalized illness with fever.

Staphylococci are the most important causative organism of **impetigo.** This is a highly contagious skin infection mostly affecting children 2 to 5 years of age, among whom it is spread by direct contact. *Streptococcus pyogenes,* a pathogen that we will be discussing shortly, can also cause impetigo, although in fewer cases. Sometimes both *S. aureus* and *S. pyogenes* are involved. *Nonbullous impetigo* (see the bulla in Figure 21.2b) is the more common form. The pathogen usually enters through some minor break in the skin. The infection can also spread to surrounding areas—a process called *autoinoculation.* Symptoms result from the host's response to the infection. The lesions eventually rupture and form light-colored crusts, as shown in Figure 21.4. Topical antibiotics are sometimes applied, but the lesions generally heal without treatment and without scarring.

The other type of impetigo, *bullous impetigo,* is caused by a staphylococcal toxin and is a localized form of staphylococcal **scalded skin syndrome.** Actually, there are two serotypes of the toxin; toxin A, which remains localized, causes bullous impetigo, and toxin B, which circulates to distant sites, causes scalded skin syndrome, as shown in Figure 21.5. Both toxins cause a separation of the skin layers, *exfoliation*. Outbreaks of bullous impetigo are a frequent problem in hospital nurseries, where the condition is known as **pemphigus neonatorum,** or *impetigo of the newborn.* (See the discussion of hexachlorophene in Chapter 7, page 188.)

Scalded skin syndrome is also characteristic of the late stages of **toxic shock syndrome (TSS).** In this potentially life-threatening condition, fever, vomiting, and a sunburnlike rash are followed by shock and sometimes organ failure, especially of the kidneys. TSS originally became known as a result of



Figure 21.5 Lesions of scalded skin syndrome. Some staphylococci produce a toxin that causes the skin to peel off in sheets, as on leg of this person. It is especially likely to occur in children under age 2.

What is the name of the toxin that produces this syndrome?

DISEASES IN FOCUS 21.1

Macular Rashes

Differential diagnosis is the process of identifying a disease from a list of possible diseases that fit the information derived from examining a patient. A differential diagnosis is important for providing initial treatment and for laboratory testing. For example, a 4-year-old boy with a history of cough, conjunctivitis, and fever (38.3°C) now has a macular rash that started on his face and neck and is spreading to the rest of his body. Use the table below to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Disease	Pathogen	Portal of Entry	Symptoms	Method of Transmission	Treatment
VIRAL DISEASES. Usually diagnosed by clinical signs and symptoms and may be confirmed by serology or PCR.					
Measles (rubeola)	Measles virus	Respiratory tract	Reddish macules first appearing on face and spreading to trunk and extremities	Aerosol	No treatment; preexposure vaccine
Rubella (German measles)	Rubella virus	Respiratory tract	Mild disease with a macular rash resembling measles, but less extensive and disappearing in 3 days or less	Aerosol	No treatment; preexposure vaccine
Fifth Disease (erythema infectiosum)	Human parvovirus B19	Respiratory tract	Mild disease with a macular facial rash	Aerosol	None
Roseola	Human herpesvirus 6, human herpesvirus 7	Respiratory tract	High fever followed by macular body rash	Aerosol	None
Hand-Foot-and-Mouth Disease	Enteroviruses	Mouth	Flat or raised rash	Aerosol; direct contact	None
FUNGAL DISEASE. Confirmed by Gram staining of skin scrapings.					
Candidiasis	*Candida albicans*	Skin; mucous membranes	Macular rash	Direct contact; endogenous infection	Miconazole, clotrimazole (topically)

staphylococcal growth associated with the use of a new type of highly absorbent vaginal tampon; the correlation is especially high for cases in which the tampons remain in place too long. A novel staphylococcal toxin called *toxic shock syndrome toxin 1 (TSST-1)* is formed at the growth site and circulates in the bloodstream. The symptoms are thought to be a result of the superantigenic properties of the toxin. (See the discussion of cytokine storms in Chapter 17.)

Today a minority of the cases of TSS are associated with menstruation. Nonmenstrual TSS occurs from staphylococcal infections that follow nasal surgery in which absorbent packing is used, after surgical incisions, and in women who have just given birth.

Streptococcal Skin Infections

Streptococci are gram-positive spherical bacteria. Unlike staphylococci, streptococcal cells usually grow in chains (see Figure 11.23, page 310). Prior to division, the individual cocci elongate on the axis of the chain, and then the cells divide (see Figure 4.1a, page 74). Streptococci cause a wide range of disease conditions beyond those covered in this chapter, including meningitis, pneumonia, sore throats, otitis media, endocarditis, puerperal fever, and even dental caries.

As streptococci grow, they secrete toxins and enzymes, virulence factors that vary with the different streptococcal species. Among these toxins are *hemolysins,* which lyse red blood cells. Depending on the hemolysin they produce, streptococci are categorized as alpha-hemolytic, beta-hemolytic, and gamma-hemolytic (actually nonhemolytic) streptococci (see Figure 6.9, page 161). Hemolysins can lyse not only red blood cells, but almost any type of cell. It is uncertain, though, just what part they play in streptococcal pathogenicity.

Beta-hemolytic streptococci are often associated with human disease. This group is further differentiated into serological groups, designated A through T, according to antigenic carbohydrates in their cell walls. The **group A streptococci (GAS),** which are synonymous with the species *Streptococcus*

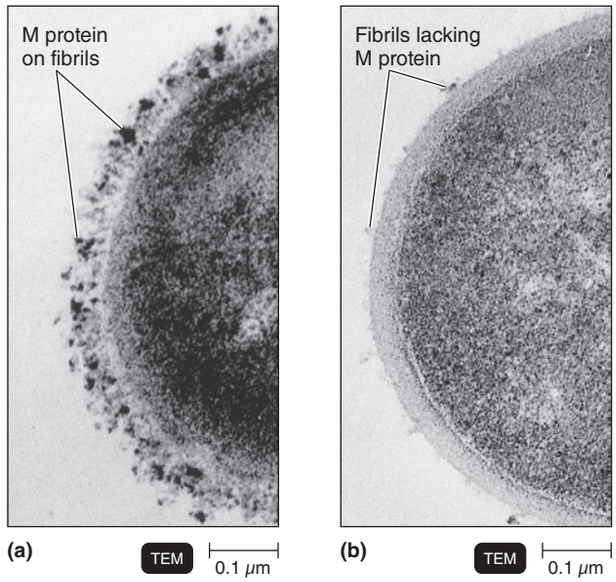


Figure 21.6 The M protein of group A beta-hemolytic streptococci. **(a)** Part of a cell that carries the M protein on a fuzzy layer of surface fibrils. **(b)** Part of a cell that lacks the M protein.

Q Is the M protein more likely to be antigenic than a polysaccharide capsule?

pyogenes, are the most important of the beta-hemolytic streptococci. They are among the most common human pathogens and are responsible for a number of human diseases—some of them deadly. These streptococci also produce certain enzymes, called *streptolysins,* that lyse red blood cells and are toxic to neutrophils. This group of pathogens is divided into over 80 immunological types according to the antigenic properties of the M protein found in some strains (Figure 21.6). This protein is external to the cell wall on a fuzzy layer of fibrils. The M protein prevents the activation of complement and allows the microbe to evade phagocytosis and killing by neutrophils (see page 449). It also appears to help the bacteria adhere to and colonize mucous membranes. Another virulence factor of the GAS is their capsule of hyaluronic acid. Exceptionally virulent strains have a mucoid appearance on blood-agar plates from heavy encapsulation and are rich in M protein. Hyaluronic acid is poorly immunogenic (it resembles human connective tissue) and few antibodies against the capsule are produced.

The GAS produce substances that promote the rapid spread of infection through tissue and by liquefying pus. Among these are *streptokinases* (enzymes that dissolve blood clots), *hyaluronidase* (an enzyme that dissolves the hyaluronic acid in the connective tissue, where it serves to cement the cells together), and *deoxyribonucleases* (enzymes that degrade DNA).

Streptococcal skin infections are generally localized, but if the bacteria reach deeper tissue, they can be highly destructive.

When *S. pyogenes* infects the dermal layer of the skin, it causes a serious disease, **erysipelas.** In this disease, the skin



Figure 21.7 Lesions of erysipelas, caused by group A beta-hemolytic streptococcal toxins.

Q What is the name of the toxin that produces skin reddening? (Hint: See Chapter 15.)

erupts into reddish patches with raised margins (Figure 21.7). It can progress to local tissue destruction and even enter the bloodstream, causing sepsis (page 639). The infection usually appears first on the face and often has been preceded by a streptococcal sore throat. High fever is common. Fortunately, *S. pyogenes* has remained sensitive to β-lactam-type antibiotics, especially cephalosporin.

Some 15,000 cases of invasive group A streptococcal infection, caused by the "flesh-eating bacteria," occur each year in the United States. The infection may be precipitated by minor breaks in the skin, and early symptoms are often unrecognized, delaying diagnosis and treatment—with serious consequences. Once established, **necrotizing fasciitis** (Figure 21.8) may destroy tissue as rapidly as a surgeon can remove it, and mortality rates



Figure 21.8 Necrotizing fasciitis due to group A streptococci. Extensive damage to the fascia (sheet of connective tissue binding the muscles) may require reconstructive surgery or even amputation of limbs.

Q What is the name of the primary toxin that leads to tissue invasion by the pathogen?

DISEASES IN FOCUS 21.2

Vesicular and Pustular Rashes



An 8-year-old boy has a rash consisting of vesicular lesions of 5 days' duration on his neck and stomach. Within 5 days, 73 students in his elementary school have an illness matching the case definition for this disease. Use the table below to provide a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.

Disease	Pathogen	Portal of Entry	Symptoms	Method of Transmission	Treatment
BACTERIAL DISEASE. Usually diagnosed by culturing the bacteria.					
Impetigo	*Staphylococcus aureus*	Skin	Vesicles on skin	Direct contact; fomites	Topical antibiotics
VIRAL DISEASES. Usually diagnosed by clinical signs and symptoms and may be confirmed by serology or PCR.					
Smallpox (variola)	Smallpox (variola) virus	Respiratory tract	Pustules that may be nearly confluent on skin	Aerosol	None
Monkeypox	Monkeypox virus	Respiratory tract	Pustules, similar to smallpox	Direct contact with or aerosols from infected small mammals	None
Chickenpox (varicella)	Varicella-zoster virus	Respiratory tract	Vesicles in most cases confined to face, throat, and trunk	Aerosol	Acyclovir for immunocompromised patients; preexposure vaccine
Shingles (herpes-zoster)	Varicella-zoster virus	Endogenous* infection of peripheral nerves	Vesicles typically on one side of waist, face and scalp, or upper chest	Recurrence of latent chickenpox infection	Acyclovir; preventive vaccine
Herpes Simplex	Herpes simplex virus type 1	Skin; mucous membranes	Vesicles around mouth; can also affect other areas of skin and mucous membranes	Initial infection by direct contact; recurring latent infection	Acyclovir

*Endogenous infections are infections caused by microorganisms already part of the host microbiota.

from systemic toxicity can exceed 40%. Streptococci are considered the most common causative organism, although other bacteria cause similar conditions. An important factor is an exotoxin produced by certain streptococcal M-protein types, *exotoxin A*, which acts as a superantigen, causing the immune system to contribute to the damage. Broad-spectrum antibiotics are usually prescribed because of the possibility that multiple bacterial pathogens are present.

Necrotizing fasciitis is often associated with **streptococcal toxic shock syndrome (streptococcal TSS),** which resembles staphylococcal TSS, described earlier in the chapter. In cases of streptococcal TSS, a rash is less likely to be present, but bacteremia is more likely to occur. M proteins shed from the surfaces of these streptococci form a complex with fibrinogen that binds to neutrophils. This causes activation of neutrophils, precipitating the release of damaging enzymes and consequent shock and organ damage. The mortality rate is much higher than with staphylococcal TSS—up to 80% has been reported.

Infections by Pseudomonads

Pseudomonads are aerobic gram-negative rods that are widespread in soil and water. Capable of surviving in any moist environment, they can grow on traces of unusual organic matter, such as soap films or cap liner adhesives used for many product containers. They are resistant to many antibiotics and disinfectants. The most prominent species is *Pseudomonas aeruginosa,* which is considered the model of an opportunistic pathogen.

Pseudomonads frequently cause outbreaks of ***Pseudomonas* dermatitis.** This is a self-limiting rash of about 2 weeks' duration, often associated with swimming pools and pool-type saunas

DISEASES IN FOCUS 21.3

Patchy Redness and Pimple-Like Conditions



An 11-month-old boy comes to a clinic with a 1-week history of an itchy red rash under his arms. The rash seems to bother him more at night, and he has no fever. Use the table below to provide a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.

Disease	Pathogen	Portal of Entry	Symptoms	Method of Transmission	Treatment
BACTERIAL DISEASES. Usually diagnosed by culturing the bacteria.					
Folliculitis	*Staphylococcus aureus*	Hair follicle	Infection of hair follicle	Direct contact; fomites; endogenous infection*	Draining of pus; topical antibiotics
Toxic Shock Syndrome	*Staphylococcus aureus*	Surgical incisions	Fever, rash, shock	Endogenous infection*	Antibiotics, depending on sensitivity profile (antibiogram)
Necrotizing Fasciitis	*Streptococcus pyogenes*	Skin abrasions	Extensive soft-tissue destruction	Direct contact	Surgical tissue removal; broad-spectrum antibiotics
Erysipelas	*Streptococcus pyogenes*	Skin; mucous membranes	Reddish patches on skin; often with high fever	Endogenous infection*	Cephalosporin
***Pseudomonas* Dermatitis**	*Pseudomonas aeruginosa*	Skin abrasions	Superficial rash	Swimming water; hot tubs	Usually self-limiting
Otitis Externa	*Pseudomonas aeruginosa*	Ear	Superficial infection of external ear canal	Swimming water	Fluoroquinolones
Acne	*Propionibacterium acnes*	Sebum channels	Inflammatory lesions originating with accumulations of sebum that rupture a hair follicle	Direct contact	Benzoyl peroxide, isotretinoin, azelaic acid
Buruli Ulcer	*Mycobacterium ulcerans*	Skin	Localized swelling or hardness progressing to deep ulcer	Contaminated water	Antimycobacterial drugs
VIRAL DISEASE. Usually diagnosed by clinical signs and symptoms.					
Warts	*Papillomavirus*	Skin	A horny projection of the skin formed by proliferation of cells	Direct contact	Removal by liquid nitrogen cryotherapy, electrodesiccation, acids, lasers
FUNGAL DISEASES. Diagnosis is confirmed by microscopic examination.					
Ringworm (tinea)	*Microsporum, Trichophyton, Epidermophyton*	Skin	Skin lesions of highly varied appearance; on scalp may cause local loss of hair	Direct contact; fomites	Griseofulvin (orally); miconazole, clotrimazole (topically)
Sporotrichosis	*Sporothrix schenkii*	Skin abrasions	Ulcer at site of infection spreading into nearby lymphatic vessels	Soil	Potassium iodide solution (orally)
PARASITIC INFESTATIONS. Diagnosis is confirmed by microscopic examination of parasite.					
Scabies	*Sarcoptes scabiei* (mite)	Skin	Papules, itching	Direct contact	Gamma benzene hexachloride, permethrin (topically)
Pediculosis (lice)	*Pediculus humanus capitis*	Skin	Itching	Primarily direct contact; possible fomites such as bedding, combs	Topical insecticide preparations

*Endogenous infections are infections caused by microorganisms already part of the host microbiota.

CLINICAL FOCUS

Infections in the Gym

As you read through this box, you will encounter a series of questions that epidemiologists ask themselves as they try to trace an outbreak to its source. Try to answer each question before going on to the next one.

1. Jason F., a 21-year-old college football player, goes to the college health center with an 11 cm × 5 cm area of redness on his right thigh. It is swollen and warm and tender when touched. His temperature is normal. He is given sulfamethoxazole-trimethoprim.
   What is Jason's probable diagnosis?
2. Jason probably has some form of bacterial skin infection, for which he is prescribed antibiotics. After 2 days, Jason returns and says the area is worse. Examination reveals a broader area of redness. He is diagnosed with cellulitis. The pustule is opened and drained.
   What do you need to do now?
3. The pus is sent to the lab for a Gram stain and a coagulase test on the culture. The results of the Gram stain and the coagulase test are shown in **Figure A** and **Figure B**, respectively.
   What is the cause of the infection?
4. The presence of gram-positive, coagulase-positive cocci indicates *Staphylococcus aureus*. The bacterium is sent for sensitivity testing.
   Why is sensitivity testing necessary?
5. Sensitivity testing is necessary to identify the antibiotic that will be most effective in killing the bacteria. The results are shown in **Figure C**. (P = penicillin, M = methicillin, E = erythromycin, V = vancomycin, X = trimethoprim-sulfamethoxazole.)
   What treatment is appropriate?
6. Based on the sensitivity testing, the most appropriate treatment is vancomycin. Over a 3-month period, 10 members of the college football and fencing teams report to the health center with cellulitis. Seven are hospitalized; one receives surgical debridement and skin grafts.
   What is the most likely source of the methicillin-resistant *Staphylococcus aureus* (MRSA)?

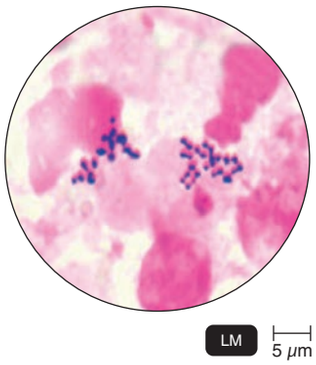


Figure A

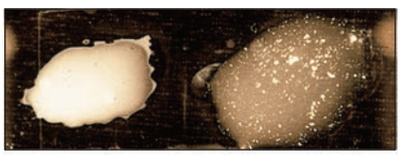


Figure B



Figure C

Although the investigations described in this report did not determine definitively the roots of MRSA transmission, three factors might have contributed to transmission in these outbreaks. First, abrasions and other skin trauma, which can facilitate entry of pathogens, are likely in some sports. Second, some sports involve frequent physical contact among players. *S. aureus* and other skin microbiota can be transmitted easily from person to person with direct contact. Third, shared equipment or other personal items that are not cleaned or laundered between users could be a vehicle for *S. aureus* transmission.

Investigation of outbreaks of MRSA among professional athletes showed that all of the infections occurred at the site of a turf burn and rapidly progressed to large abscesses that required surgery to drain. MRSA was recovered from whirlpools and taping gel and from 35 of the 84 nasal swabs from players and staff members.

The CDC recommends cleaning locker rooms and shared equipment with detergent-based cleaners to prevent MRSA infections.

Source: Adapted from *MMWR* 58(3):52–55, updated 2013.

and hot tubs. When many people use these facilities, the alkalinity rises, and the chlorines become less effective; at the same time, the concentration of nutrients that support the growth of pseudomonads increases. Hot water causes hair follicles to open wider, facilitating the entry of bacteria. Competition swimmers are often troubled with **otitis externa,** or "*swimmer's ear,*" a painful infection of the external ear canal leading to the eardrum that is frequently caused by pseudomonads.

P. aeruginosa produces several exotoxins that account for much of its pathogenicity. It also produces an endotoxin. *P. aeruginosa* often grows in dense biofilms that contribute to its frequent identification as a cause of healthcare-associated infections of indwelling medical tubes or devices. This bacterium is also a serious opportunistic pathogen for patients with the genetic lung disease cystic fibrosis; biofilm formation plays a prominent part in this.

P. aeruginosa is also a very common and serious opportunistic pathogen in burn patients, particularly those with second- and third-degree burns. Infection may produce blue-green pus, whose color is caused by the bacterial pigment **pyocyanin.** Of concern in many hospitals is the ease with which *P. aeruginosa* grows in flower vases, mop water, and even dilute disinfectants.

The relative resistance to antibiotics that characterizes pseudomonads is still a problem. However, in recent years, several new antibiotics have been developed, and chemotherapy to treat these infections is not as restricted as it once was. The quinolones and the newer, antipseudomonal β-lactam antibiotics are the usual drugs of choice. Silver sulfadiazine is very useful in the treatment of burn infections by *P. aeruginosa.*

Buruli Ulcer

Buruli ulcer, named for a now-renamed region of Uganda in Africa, is an emerging disease found primarily in western and central Africa. Although widespread in tropical Africa, it was first accurately described in Australia in 1948 and since then has been reported in localized tropical and temperate areas around the globe—including Mexico and areas of South America. The disease is caused by *Mycobacterium ulcerans,* which is similar to the mycobacteria that cause tuberculosis and leprosy. When the pathogen is introduced into the skin, it causes a disease that progresses slowly with few serious early signs or symptoms. Eventually, however, the result is a deep ulcer that often becomes massive and seriously damaging. Untreated, this can be so extensive as to require amputation or plastic surgery. This tissue damage is attributed to the production of a toxin, *mycolactone.* Epidemiologically, the infection is associated with contact with swamps and slow-flowing waters. The pathogen probably enters through a break in the skin from a minor cut or insect bite.

Buruli ulcer incidence has increased and now exceeds incidence of leprosy and, in some areas, even tuberculosis. The World Health Organization recently identified it as a global threat to public health.

Buruli ulcer is diagnosed primarily by the appearance of the ulcer, although awareness is higher in endemic areas, and is treated by antimycobacterial drugs such as streptomycin-rifampicin combinations.

Acne

Acne is probably the most common skin disease in humans, affecting an estimated 17 million people in the United States. More than 85% of all teenagers have the problem to some degree. Acne can be classified by type of lesion into three categories: comedonal acne, inflammatory acne, and nodular cystic acne. They require different treatments.

Normally, skin cells that are shed inside the hair follicle are able to leave, but acne develops when cells are shed in higher than normal numbers, combine with sebum, and the mixture clogs the follicle. As sebum accumulates, whiteheads (comedos) form; if the blockage protrudes through the skin, a blackhead (comedone) forms. The dark color of blackheads is due not to dirt, but to lipid oxidation and other causes. Topical agents do not affect sebum formation, which is a root cause of acne and depends on hormones such as estrogens or androgens. Diet has no known effect on sebum production, but pregnancy, some hormone-based contraceptive methods, and hormonal changes with age do reduce sebum formation and influence acne.

Comedonal (mild) acne is usually treated with topical agents such as azelaic acid (Azelex), salicyclic acid preparations, or retinoids (which are derivatives of vitamin A, such as tretinoin, tazarotene [Tazorac], or adapalene [Differin]). These topical agents do not affect sebum formation.

Inflammatory (moderate) acne arises from bacterial action, especially *Propionibacterium acnes,* an anaerobic diphtheroid commonly found on the skin. *P. acnes* has a nutritional requirement for glycerol in sebum; in metabolizing the sebum, it forms free fatty acids that cause an inflammatory response. Neutrophils that secrete enzymes that damage the wall of the hair follicle are attracted to the site. The resulting inflammation leads to the appearance of pustules and papules. At this stage, therapy is usually focused on preventing formation of sebum; topical agents are not effective for this.

Inflammatory acne can also be treated by targeting *P. acnes* with antibiotics. The familiar nonprescription acne treatments containing benzoyl peroxide are effective against some bacteria, especially *P. acnes,* and also cause drying that helps loosen plugged follicles. Benzoyl peroxide is also available as a gel and in products where it is combined with antibiotics such as clindamycin (BenzaClin) and erythromycin (Benzamycin). A relatively new treatment available by prescription, Epiduo, is a topical gel containing the combination of adapalene and benzoyl peroxide.

Alternatives to chemical treatments have been approved by the U.S. Food and Drug Administration (FDA) for treatment of mild to moderate acne. The Clear Light system, which bathes the skin with high-intensity blue light (405–420 nm), and Smoothbeam treatment, which uses laser light, penetrate the

Clinical Case

The similarity in the siblings' rashes prompts Molly to reexamine her records and obtain more detailed information about the children who came to her office with comparable rashes.

After speaking to the childrens' parents, Molly learns that all five children have been to the same community swimming pool in the past 72 hours. Molly notifies the health department; they contact the only other general medical practice in this small town and obtain a list of similar cases. In these cases, the patients have rashes on the chest and abdomen (90%), buttocks (67%), arms (71%), legs (86%), and also the hands, feet, and head and neck.

What pathogens can cause itchy, pimple-like rashes?

581 589 595 597 603



Figure 21.9 Severe acne.

Q Isotretinoin often leads to dramatic improvement for cases of severe acne, but what precautions must be observed?

skin surface to speed healing and prevent pimples from forming. Also approved is a handheld device, ThermaClear, which delivers a brief pulse of heat to the lesions.

Some patients with acne progress to **nodular cystic (severe) acne.** Nodular cystic acne is characterized by nodules or cysts, which are inflamed lesions filled with pus deep within the skin (Figure 21.9). These leave prominent scars on the face and upper body, which often leave psychological scars as well. An effective treatment for cystic acne is isotretinoin, which reduces the formation of sebum. Under the trade name of Accutane, its distribution in the United States has been discontinued by the manufacturer. It is, however, distributed outside this country under the name Roaccutane. Anyone considering the use of the drug should be warned that it is highly *teratogenic,* meaning it can cause serious damage to the developing fetus in a pregnant woman. Other side effects may include inflammatory bowel disease and ulcerative colitis.

CHECK YOUR UNDERSTANDING

- Which bacterial species features the virulence factor M protein? 21-3
- What is the common name for otitis externa? 21-4

Viral Diseases of the Skin

Many viral diseases, although systemic and transmitted by respiratory or other routes, are most apparent by their effects on the skin. Although not always very significant in adults, several of these diseases, such as rubella, chickenpox, fifth disease, and herpes simplex, can cause serious damage in a developing fetus.

Warts

Warts, or papillomas, are generally benign skin growths caused by viruses. It was long known that warts can be transmitted from one person to another by contact, even sexually, but it was not until 1949 that viruses were identified in wart tissues. More than 50 types of *papillomavirus* are now known to cause different kinds of warts, often with greatly varying appearances.

After infection, there is an incubation period of several weeks before the warts appear. The most common medical treatments for warts are to apply extremely cold liquid nitrogen (cryotherapy), dry them with an electrical current (electrodesiccation), or burn them with acids. There is evidence that compounds containing salicylic acids are especially effective. Topical application of prescription drugs such as podofilox or imiquimod (Aldara) is often effective; the latter stimulates production of antiviral interferons. Warts that do not respond to any other treatments can be treated with lasers or injected with bleomycin, an antitumor drug.

Although warts are not a form of cancer, some skin and cervical cancers are associated with certain papillomaviruses. The incidence of genital warts (see Chapter 26) has reached epidemic proportions.

Smallpox (Variola)

During the Middle Ages, an estimated 80% of the population of Europe contracted **smallpox*** at some time during their lives. Those who recovered from the disease retained disfiguring scars. The disease, introduced by American colonists, was even more devastating to Native Americans, who had had no previous exposure and thus little resistance.

Smallpox is caused by an orthopoxvirus known as the smallpox (variola) virus. There are two basic forms of this disease: **variola major,** with a mortality rate of 20% or higher, and **variola minor,** with a mortality rate of less than 1%.

Transmitted by the respiratory route, the viruses infect many internal organs before they eventually move into the bloodstream, infecting the skin and producing more recognizable symptoms. The growth of the virus in the epidermal layers of the skin causes lesions that become pustular after 10 days or so (Figure 21.10).

Smallpox was the first disease to which immunity was artificially induced (see pages 10 and 487) and the first to be eradicated from the human population. The last victim of a natural case of smallpox is believed to be an individual who recovered from variola minor in 1977 in Somalia. (However, 10 months after this case, there was a smallpox fatality in England caused by escape of the virus from a hospital research laboratory.) The eradication of smallpox was possible because an effective vaccine was developed and because there are no animal host reservoirs for the disease. A concerted worldwide vaccination effort was coordinated by the World Health Organization.

*The origin of the name *smallpox* reportedly arose in the late fifteenth century in France, where syphilis had just been introduced. These patients exhibited a severe skin rash called *la grosse verole,* or "the great pox." The rash was compared with that of an endemic disease of the time, which was then referred to as *la petite verole,* or "the small pox." In English, the endemic disease became known as smallpox.



Figure 21.10 Smallpox lesions. In some severe cases, the lesions nearly run together (are confluent).

Q How do these lesions differ from chickenpox?

Today, only two sites are known to maintain the smallpox virus, one in the United States and one in Russia. Dates for the destruction of these collections have been set and then postponed.

Smallpox would be an especially dangerous agent for bioterrorism. Vaccination in the United States ended in the early 1970s. People who were vaccinated prior to that time have waning immunity; however, they probably have some remaining protection that would at least moderate the disease. Stocks of smallpox vaccine are being accumulated as a precaution. No general vaccination program of the entire population is contemplated. However, certain groups, among them military and health care workers, may be an exception. Administered to the general population, the vaccine would cause a significant number of deaths, especially among immunosuppressed individuals.

Complications from the smallpox vaccine can be treated with vaccinia immune globulin, which contains antibodies to the virus. The investigational antiviral drug, cidofovir, can also be administered.

With the disappearance of smallpox, there has been some concern with a similar disease, **monkeypox.** This disease first appeared among zoo monkeys that originated in Africa and east Asia and is endemic there in small animals. There are occasional outbreaks among humans in those areas, and one outbreak of more than 50 cases in the United States in 2003 was attributed to contact with pet prairie dogs. These animals apparently were infected by being housed in pet stores with Gambian giant rats imported from western Africa. Monkeypox closely resembles smallpox in symptoms and, while smallpox was endemic, was probably mistaken for it. The mortality rate is typically 1–10% in African adults, highest in children. There were no deaths in the U.S. outbreak. The *monkeypox virus,* like smallpox virus, is an orthopoxvirus, and vaccination for smallpox has a protective effect. Monkeypox is known to jump from animals to humans, but fortunately its transmission from human to human has been very limited. The World Health Organization is monitoring recent outbreaks to see whether human-to-human transmission increases.

Chickenpox (Varicella) and Shingles (Herpes Zoster)

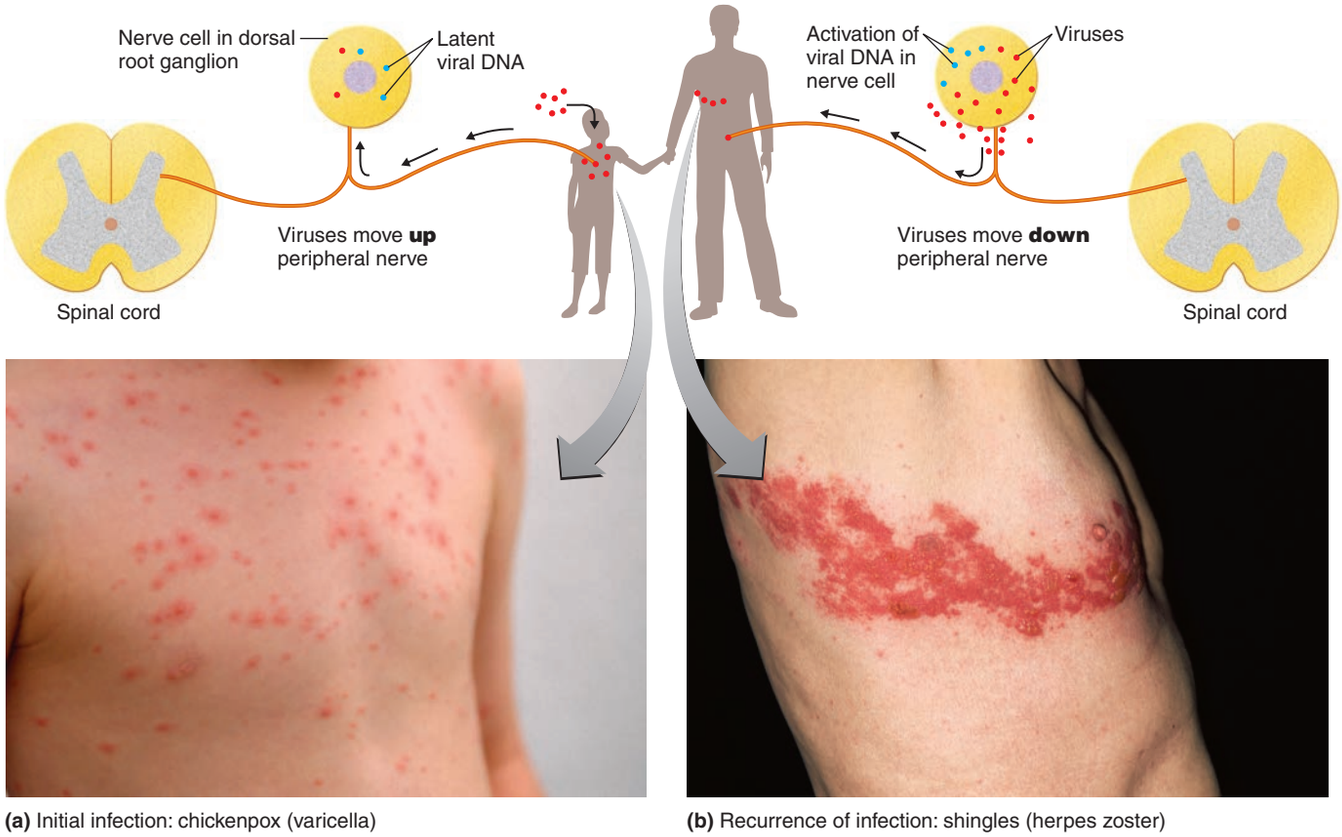
Chickenpox (*varicella*) is a relatively mild disease when contracted, as it usually is, in childhood. The mortality rate from chickenpox is very low and is usually from complications such as encephalitis (infection of the brain) or pneumonia. Almost half of such deaths occur in adults.

Chickenpox (**Figure 21.11a**) is the result of an initial infection with the *herpesvirus varicella-zoster.* (The official, but less used, name is *human herpesvirus 3;* see Chapter 13). The disease is acquired when the virus enters the respiratory system, and the infection localizes in skin cells after about 2 weeks. The infected skin is vesicular for 3 to 4 days. During that time, the vesicles fill with pus, rupture, and form a scab before healing. Lesions are mostly confined to the face, throat, and lower back but can also occur on the chest and shoulders. If varicella infection occurs during early pregnancy, serious fetal damage may occur in about 2% of cases.

Reye's syndrome is an occasional severe complication of chickenpox, influenza, and some other viral diseases. A few days after the initial infection has receded, the patient persistently vomits and exhibits signs of brain dysfunction, such as extreme drowsiness or combative behavior. Coma and death can follow. At one time, the death rate of reported cases approached 90%, but this rate has been declining with improved care and is now 30% or lower when the disease is recognized and treated in time. Survivors may show neurological damage, especially if very young. Reye's syndrome affects children and teenagers almost exclusively. The use of aspirin to lower fevers in chickenpox and influenza increases the chances of acquiring Reye's syndrome.

Like all herpesviruses, a characteristic of varicella-zoster virus is its ability to remain latent within the body. Following a primary infection, the virus enters the peripheral nerves and moves to a central nerve ganglion (a group of nerve cells lying outside the central nervous system), where it persists as viral DNA. Humoral antibodies cannot penetrate into the nerve cell, and because no viral antigens are expressed on the surface of the nerve cell, cytotoxic T cells are not activated. Therefore, neither arm of the specific immune system disturbs the latent virus.

Latent varicella-zoster virus is located in the dorsal root ganglion near the spine. Later, perhaps as long as decades later, the virus may be reactivated (Figure 21.11b). The trigger can be stress or simply the lower immune competence associated with aging. The virions produced by the reactivated DNA move along the peripheral nerves to the cutaneous sensory nerves of the skin, where they cause a new outbreak of the virus in the form of **shingles** (*herpes zoster*).



(a) Initial infection: chickenpox (varicella)

(b) Recurrence of infection: shingles (herpes zoster)

Figure 21.11 Chickenpox (varicella) and shingles (herpes zoster). **(a)** Initial infection with the virus, usually during childhood, causes chickenpox. The lesions are vesicles, eventually becoming pustules that rupture and form scabs. The virus then moves to a dorsal root ganglion near the spine, where it remains latent indefinitely. **(b)** Later, usually in late adulthood, the latent virus becomes reactivated, causing shingles. Reactivation can be caused by stress or weakening of the immune system. The skin lesions are vesicles.

Q Does the photo in (a) illustrate an early or late stage of chickenpox?

Shingles is simply a different expression of the virus that causes chickenpox: different because the patient, having had chickenpox, now has partial immunity to the virus. Exposing children to shingles has led to their contracting chickenpox. Shingles seldom occurs in people under age 20, and by far the highest incidence is among older adults. It is unusual for a patient to develop shingles more than once.

In shingles, vesicles similar to those of chickenpox occur but are localized in distinctive areas. Typically, they are distributed about the waist (the name *shingles* is derived from the Latin *cingulum,* for girdle or belt), although facial shingles and infections of the upper chest and back also occur (see Figure 21.11b). The infection follows the distribution of the affected cutaneous sensory nerves and is usually limited to one side of the body at a time because these nerves are unilateral. Occasionally, such nerve infections can result in nerve damage that impairs vision or even causes paralysis. Severe burning or stinging pain is a frequent symptom; occasionally this persists for months or years, a condition called *postherpetic neuralgia.*

The antiviral drugs acyclovir, valacyclovir, and famciclovir are approved for treatment of shingles. For immunocompromised patients, in which a mortality rate of 17% is reported, and patients with ocular involvement, treatment with antivirals is mandatory.

A live, attenuated varicella vaccine was licensed in 1995. Since then, cases of the disease have declined steadily. There is evidence that the effectiveness of the vaccine, which is about 97% at outset, declines with time. The lack of a booster effect from exposure to new cases of varicella is a factor in this. Therefore, varicella in previously vaccinated persons, called **breakthrough varicella,** is becoming fairly common. Because the vaccine is at least partially effective, it is a relatively mild disease with a rash that does not look much like typical varicella. A booster dose of the vaccine may eventually be needed for complete control of varicella.

Another concern is that the waning effectiveness of the childhood vaccination will lead to a population of susceptible adults, for whom the disease tends to be more severe. Therefore, the current recommendation is that adults 60 years of age or older receive a newly approved *zoster vaccine* even if the subject has had chickenpox or shingles previously.



Figure 21.12 Cold sores, or fever blisters, caused by herpes simplex virus. Lesions are located mainly at the margin of the red area of the lips.

Q Why can cold sores reappear, and why do they recur in the same place?

Herpes Simplex

Herpes simplex viruses (HSV) can be separated into two identifiable groups, HSV-1 and HSV-2. The name *herpes simplex virus,* used here, is the common or vernacular name. The official names are *human herpesvirus 1* and *2.* HSV-1 is transmitted primarily by oral or respiratory routes, and infection usually occurs in infancy. Serological surveys show that about 90% of the U.S. population has been infected. Frequently, this infection is subclinical, but many cases develop lesions known as **cold sores** or **fever blisters.** These are painful, short-lived vesicles that occur near the outer red margin of the lips (**Figure 21.12**).

Cold sores, caused by herpesvirus infections, are often confused with **canker sores.** The cause of canker sores is unknown, but their occurrence is often related to stress or menstruation. While similar to cold sores in appearance, canker sores usually appear in different areas. They occur as painful sores on movable mucous membranes, such as those on the tongue, cheeks, and inner surface of the lips. They ordinarily heal in a few days but often recur.

HSV-1 usually remains latent in the trigeminal nerve ganglia communicating between the face and the central nervous system (**Figure 21.13**). Recurrences can be triggered by events such as excessive exposure to ultraviolet radiation from the sun, emotional upsets, or the hormonal changes associated with menstruation.

HSV-1 infection can be transmitted by skin contact among wrestlers; this is colorfully termed **herpes gladiatorum.** Incidence as high as 3% has been reported among high school wrestlers. Nurses, physicians, and dentists are occupationally susceptible to **herpetic whitlow,** infections of the finger caused by contact with HSV-1 lesions—as are children with herpetic oral ulcers.

A very similar virus, HSV-2, is transmitted primarily by sexual contact. It is the usual cause of genital herpes (see Chapter 26). HSV-2 is differentiated from HSV-1 by its antigenic makeup and by its effect on cells in tissue culture. It is latent in the sacral nerve ganglia found near the base of the spine, a different location from that of HSV-1.

Very rarely, either type of the herpes simplex virus may spread to the brain, causing **herpes encephalitis.** Infections by HSV-2 are more serious, with a fatality rate as high as 70% if untreated. Only about 10% of survivors can expect to lead healthy lives. When administered promptly, acyclovir often cures such encephalitis. Even so, the mortality rate in certain outbreaks is still 28%, and only 38% of the survivors escape serious neurological damage.

Measles (Rubeola)

Measles (**rubeola**) is an extremely contagious viral disease spread by the respiratory route. Because a person with measles is infectious before symptoms appear, quarantine is not an effective measure of prevention.

The measles vaccine, now usually administered as the MMR vaccine (measles, mumps, rubella), has almost eliminated measles in the United States. Since the vaccine's introduction measles cases have declined from an estimated 5 million cases a year to virtual disappearance. As with smallpox, there is no animal reservoir for measles, but because the virus is so much more infectious than smallpox, herd immunity is difficult to obtain. Therefore, the present worldwide target is to control measles by vaccination, rather than eradication. This approach has met with some success; compared to an estimated 873,000 deaths worldwide in 1999, there were 158,000 in 2012. The goal is a

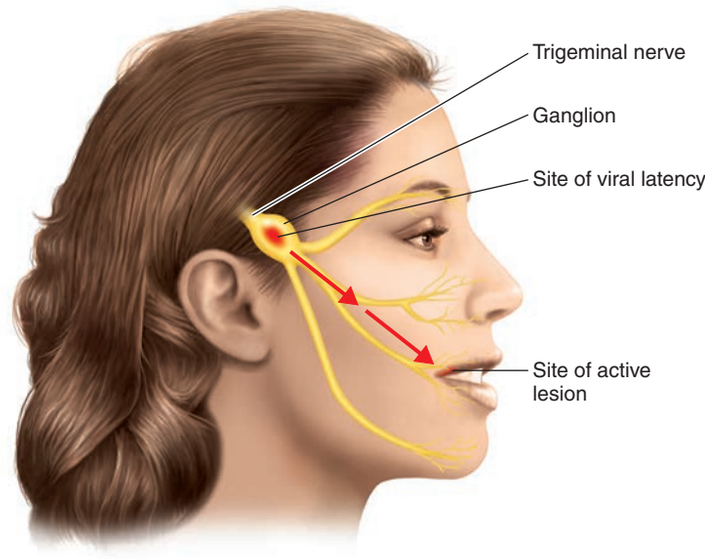


Figure 21.13 Site of latency of herpes simplex type 1 in the trigeminal nerve ganglion.

Q Why is this nerve system called *trigeminal*?



Figure 21.14 The rash of small raised spots typical of measles (rubeola). The rash usually begins on the face and spreads to the trunk and extremities.

Q Why is it potentially possible to eradicate measles?

further 95% reduction in mortality by 2015. (See the Clinical Focus box in Chapter 18.)

Although the vaccine is about 95% effective, cases continue to occur among people who do not develop or retain good immunity. Some of these infections are caused by contact with infected people from outside the United States.

An unexpected result of the measles vaccine is that many cases of measles today occur in children under the age 1. Measles is especially hazardous to infants, who are more likely to have serious complications. In prevaccination days, measles was rare at this age because infants were protected by maternal antibodies derived from their mothers' recovery from the disease. Unfortunately, maternal antibodies made in response to the vaccine are not as effective in providing protection as are antibodies made in response to the disease. Because the vaccine is not effective when administered in early infancy, the child does not receive the initial vaccination before 12 months. Therefore, the child is vulnerable for a significant time.

Similar to smallpox and chickenpox, infection begins in the upper respiratory system. After an incubation period of 10 to 12 days, symptoms develop resembling those of a common cold. Soon, a macular rash appears, beginning on the face and spreading to the trunk and extremities (Figure 21.14). Measles lesions of the oral cavity include *Koplik's spots,* small red spots with central blue-white specks, on the oral mucosa opposite the molars. The presence of Koplik's spots is a diagnostic indicator of measles. Serological tests conducted a few days after appearance of the rash can be used to confirm the diagnosis. (See also Diseases in Focus 21.1.)

Measles is an extremely dangerous disease, especially in infants and very old people. It is frequently complicated by middle ear infections or pneumonia caused by the virus itself or by a secondary bacterial infection. Encephalitis strikes approximately 1 in 1000 measles victims; its survivors are often left with permanent brain damage. As many as 1 in 3000 cases is fatal, mostly in infants. A rare complication of measles (about 1 in 1,000,000 cases) is **subacute sclerosing panencephalitis.** Occurring mostly in men, it appears about 1 to 10 years after recovery from measles. Severe neurological symptoms result in death within a few years.

Rubella

Rubella, or *German measles* (so called because it was first described by German physicians in the eighteenth century), is a much milder viral disease than rubeola (measles) and often goes undetected. A macular rash of small red spots and a light fever are the usual symptoms (Figure 21.15). Complications are rare, especially in children, but encephalitis occurs in about 1 case in 6000, mostly in adults. The *rubella virus* is transmitted by the respiratory route, and an incubation of 2 to 3 weeks is the norm. Recovery from clinical or subclinical cases appears to give a firm immunity.

The seriousness of rubella was not appreciated until 1941, when certain severe birth defects were associated with maternal infection during the first trimester (3 months) of pregnancy, a condition called **congenital rubella syndrome.** If a pregnant



Figure 21.15 The rash of red spots characteristic of rubella. The spots are not raised above the surrounding skin.

Q What is congenital rubella syndrome?

woman contracts the disease during this time, there is about a 35% incidence of serious fetal damage, including deafness, eye cataracts, heart defects, mental retardation, and death. Some 15% of babies with congenital rubella syndrome die during their first year. The last major epidemic of rubella in the United States was during 1964 and 1965. At least 20,000 severely impaired children were born during that epidemic.

It is therefore important to identify women of childbearing age who are not immune to rubella. In some states, the blood test required for a marriage license includes a test for rubella antibodies. Serum antibody can be assayed by a number of commercially available laboratory tests. Accurate diagnosis of immune status always requires such tests, because histories alone are unreliable.

In addition to this surveillance, a rubella vaccine was introduced in 1969. Follow-up studies indicate that more than 90% of vaccinated individuals are protected for at least 15 years. Because of these preventive measures, fewer than 10 annual cases of congenital rubella syndrome are now reported.

The vaccine is not recommended for pregnant women. However, in hundreds of cases in which women were vaccinated 3 months before or 3 months after their presumed date of conception, no case of congenital rubella syndrome defects has occurred.

Other Viral Rashes

Fifth Disease (Erythema Infectiosum) Parents with young children are often baffled by a diagnosis of fifth disease, which they have never heard of before. The name derives from a 1905 list of skin rash diseases: measles, scarlet fever, rubella, Filatov Dukes' disease (a mild form of scarlet fever), and the fifth disease on the list. This **fifth disease,** or **erythema infectiosum,** produces no symptoms at all in about 20% of individuals infected by the virus (*human parvovirus B19,* first identified in 1989). Symptoms are similar to a mild case of influenza, but there is a distinctive "slapped-cheek" facial rash that slowly fades. In adults who missed an immunizing infection in childhood, the disease may cause anemia, an episode of arthritis, or, rarely, miscarriage.

Roseola **Roseola** is a mild, very common childhood disease. The child has a high fever for a few days, which is followed by a rash over much of the body lasting for a day or two. Recovery leads to immunity. The pathogens are *human herpesviruses 6 (HHV-6)* and 7 *(HHV-7)*—the latter is responsible for 5–10% of roseola cases. Both viruses are present in the saliva of most adults.

Hand-Foot-and-Mouth Disease Caused by several enteroviruses, hand-foot-and-mouth disease is spread by contact with mucous or saliva of an infected person. It most commonly occurs among children in day care, preschool, and kindergarten. Limited epidemics can occur, especially during summer and fall. The usual incubation is 3–7 days, with initial symptoms of fever followed by sore throat. Soon after, a rash (either flat or raised) appears on areas such as the hands, feet, mouth, tongue, and interior cheeks. It is rare for patients to require hospitalization, but occasionally—when the disease is caused by *Enterovirus* 71—it can be accompanied by neurological conditions such as encephalitis, meningitis, and even a paralysis resembling polio. Adults with normal immune systems are less likely to be infected. There is no treatment.

CHECK YOUR UNDERSTANDING

How did the odd naming of "fifth disease" arise? **21-5**

Fungal Diseases of the Skin and Nails

As mentioned previously the skin is most susceptible to microorganisms that can resist high osmotic pressure and low moisture. It is not surprising, therefore, that fungi cause a number of skin disorders. Any fungal infection of the body is called a **mycosis.**

Cutaneous Mycoses

Fungi that colonize the hair, nails, and the outer layer (stratum corneum) of the epidermis (see Figure 21.1) are called **dermatophytes;** they grow on the keratin present in those locations. Termed **dermatomycoses,** these fungal infections are more informally known as *tineas* or *ringworm.* **Tinea capitis,** or ringworm of the

Clinical Case

Staphylococcus aureus, herpesviruses, and *Pseudomonas aeruginosa* are likely causes of community-acquired infections. To find a control group, the health department asks each case to name up to two adults and two children who were in the pool at the same time but did not develop a rash. A parent/guardian was asked in the case of children.

In all, 26 cases and four controls are identified. The health department obtains swabs from the rashes and has them inoculated onto nutrient agar and incubated at 35°C for 24 hours. The resulting growth on the Petri plate is shown in the photo below.



Based on the figure, what is the bacterium?



(a) Ringworm (Tinea barbae)



(b) Athlete's foot (Tinea pedis)

Figure 21.16 Dermatomycoses.

Q Is ringworm caused by a helminth?

scalp, is fairly common among elementary school children and can result in bald patches. The infections tend to expand circularly, hence the term *ringworm* (Figure 21.16a). The infection is usually transmitted by contact with fomites. Dogs and cats are also frequently infected with fungi that cause ringworm in children. Ringworm of the groin, or jock itch, is known as **tinea cruris,** and ringworm of the feet, or athlete's foot, is known as **tinea pedis** (Figure 21.16b). The moisture in such areas favors fungal infections. Ringworm of the fingernails or toenails is called **tinea unguium,** or *onychomycosis*.

Three genera of fungi are involved in cutaneous mycosis. *Trichophyton* (trik-ō-FĪ-ton) can infect hair, skin, or nails; *Microsporum* (mī-krō-SPOR-um) usually involves only the hair or skin; *Epidermophyton* (ep′i-der-mō-FĪ-ton) affects only the skin and nails. The topical drugs available without prescription for tinea infections include miconazole and clotrimazole. Athlete's foot is often difficult to cure. Topical allylamine preparations containing terbinafine or naftifine, as well as another allylamine, butenavine, are recommended and are now available without a prescription. Extended application is usually required. When hair is involved, topical treatment is not very effective. An oral antibiotic, griseofulvin, is often useful in such infections because it can localize in keratinized tissue, such as skin, hair, or nails. When nails are infected, oral itraconazole and terbinafine are the drugs of choice, but treatment may require weeks and both must be used with caution because of potential severe side effects.

Subcutaneous Mycoses

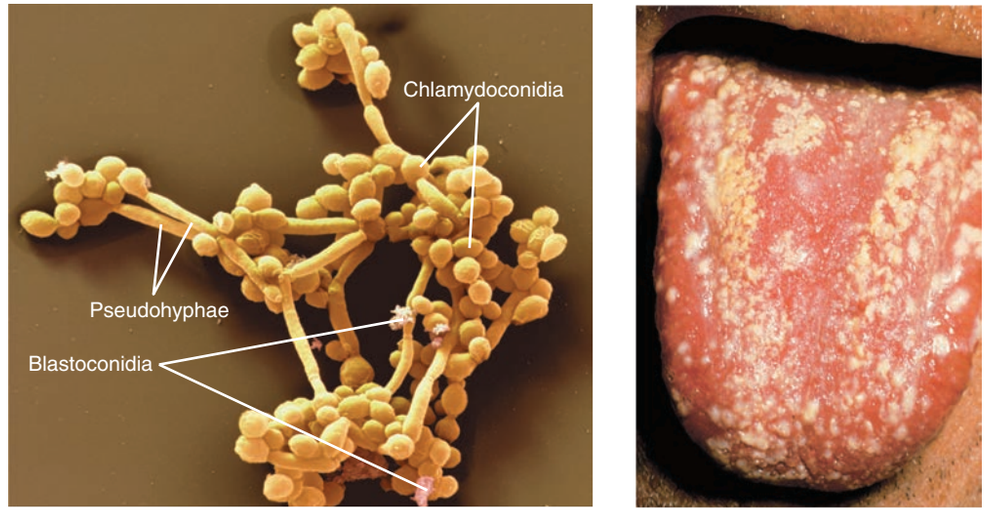
Subcutaneous mycoses are more serious than cutaneous mycoses. Even when the skin is broken, cutaneous fungi do not seem to be able to penetrate past the stratum corneum, perhaps because they cannot obtain sufficient iron for growth in the epidermis and the dermis. Usually subcutaneous mycoses are caused by fungi that inhabit the soil, especially decaying vegetation, and penetrate the skin through a small wound that allows entry into subcutaneous tissues.

In the United States, the most common disease of this type is **sporotrichosis,** caused by the dimorphic fungus *Sporothrix schenkii*. Most cases occur among gardeners or other people working with soil. The infection frequently forms a small ulcer on the hands. The fungus often enters the lymphatic system in the area and there forms similar lesions. The condition is seldom fatal and is effectively treated by ingesting a dilute solution of potassium iodide, even though the organism is not affected in vitro by even a 10% solution of potassium iodide.

Candidiasis

The bacterial microbiota of the mucous membranes in the genitourinary tract and mouth usually suppress the growth of such fungi as *Candida albicans*. Several other species of *Candida,* for example *C. tropicalis* or *C. krusei* (KROO-sē-ē), may also be involved. The morphology of these organisms is not always yeastlike but can exhibit the formation of pseudohyphae, long cells that resemble hyphae. In this form, *Candida* is resistant to phagocytosis, which may be a factor in its pathogenicity (Figure 21.17a). Because the fungus is not affected by antibacterial drugs, it sometimes overgrows mucosal tissue when antibiotics suppress the normal bacterial microbiota. Changes in the normal mucosal pH may have a similar effect. Such overgrowths by *C. albicans* are called **candidiasis.** Newborn infants, whose normal microbiota have not become established, often suffer from a whitish overgrowth of the oral cavity, called **thrush** (Figure 21.17b). *C. albicans* is also a very common cause of vaginitis (see Chapter 26).

Immunosuppressed individuals, including AIDS patients, are unusually prone to *Candida* infections of the skin and mucous membranes. On people who are obese or diabetic, the areas of the skin with more moisture tend to become infected with this fungus. The infected areas become bright red, with lesions on the borders. Skin and mucosal infections by *C. albicans* are usually treated with topical applications of miconazole, clotrimazole, or nystatin. If candidiasis becomes systemic, as can happen in immunosuppressed individuals, *fulminating disease* (one that



(a) *Candida albicans* **(b)** Oral candidiasis, or thrush

Figure 21.17 Candidiasis. **(a)** *Candida albicans.* Notice the spherical chlamydoconidia (resting bodies formed from hyphal cells) and the smaller blastoconidia (asexual spores produced by budding) (see Chapter 12). **(b)** This case of oral candidiasis, or thrush, produced a thick, creamy coating on the tongue.

Q How can antibacterial drugs lead to candidiasis?

appears suddenly and severely) and death can result. The usual drug of choice to treat systemic candidiasis is fluconazole. Several new treatments are now also available; for example, some of the new echinocandin class antifungals, such as micafungin and anidulafungin, are now approved for this use.

CHECK YOUR UNDERSTANDING

- How do sporotrichosis and tineas differ? How are they similar? **21-6**
- How might penicillin use result in candidiasis? **21-7**

Parasitic Infestation of the Skin

Parasitic organisms such as some protozoa, helminths, and microscopic arthropods can infest the skin and cause disease conditions. We will describe two examples of common arthropod infestation, scabies and lice.

Scabies

Probably the first documented connection between a microscopic organism (330–450 μm) and a disease in humans was **scabies,** which was described by an Italian physician in 1687. The disease involves intense local itching and is caused by the tiny mite *Sarcoptes scabiei* burrowing under the skin to lay its eggs (**Figure 21.18**). The burrows are often visible as slightly elevated, serpentine lines about 1 mm in width. However, scabies may appear as a variety of inflammatory skin lesions, many of them secondary infections from scratching. The mite is transmitted by intimate contact, including sexual contact, and is most often seen in family members, nursing home residents, and teenagers infected by children for whom they baby-sit.

About 500,000 people seek treatment for scabies in the United States each year; in developing countries, it is even more prevalent. The mite lives about 25 days, but by that time eggs

Clinical Case

P. aeruginosa is isolated from the 26 cases that were tested. The health department obtains samples of pool water and takes environmental swabs from the tile around the pool and from an 18-foot inflatable device from the children's pool. The samples are cultured on nutrient agar. Water chlorination is adequate; the water tests negative for bacteria. *P. aeruginosa* is found on the tile at the shallow end of the pool and on the inflatable. Twenty-five of the patients with rashes and none of the controls had used the inflatable.

The inflatable is not watertight; during use, inflation is maintained with an air pump. The inflatable is used about 1 hour a day, 3 days a week, and stored next to the pool when not in use. Water is visibly seeping from the seams of the inflatable.

Why is *P. aeruginosa* a likely candidate for this type of infection?



Figure 21.18 Scabies mites in skin.

Would a microscope be required to identify this pathogen?

have hatched and produced a dozen or so progeny. Scabies is usually diagnosed by microscopic examination of skin scrapings and usually is treated by topical application of permethrin. Difficult cases are sometimes treated with oral ivermectin.

Pediculosis (Lice)

Infestations by lice, called **pediculosis,** have afflicted humans for thousands of years. Although usually associated in the public mind with poor sanitation, outbreaks of head lice among middle- and upper-class schoolchildren in the United States are common. Parents are usually appalled, but head lice are easily transferred by head-to-head contact, such as occurs among children who know each other well. The head louse, *Pediculus humanus capitis,* is not the same as the body louse, *Pediculus humanus corporis.* These are subspecies of *Pediculus humanus* that have adapted to different areas of the body. Only the body louse spreads diseases, such as epidemic typhus.

Lice (see Figure 12.32a, page 352) require blood from the host and feed several times a day. The victim is often unaware of these silent passengers until itching, which is a result of sensitization to louse saliva, develops several weeks later. Scratching can result in secondary bacterial infections. The head louse has legs especially adapted to grasp scalp hairs (**Figure 21.19a**). During a life span of a little over a month, the female louse produces several eggs (nits) a day. The eggs are attached to hair shafts close to the scalp (Figure 21.19b) to benefit from a warmer incubation temperature, and they hatch in about a week. The very young stages of the louse are also called nits. Empty egg cases are whitish and more visible. They do not necessarily indicate the presence of live lice. As the hair grows (at the rate of about 1 cm a month), the attached nit moves away from the scalp.

A point of interest is that in the United States, lice have become adapted to the cylindrical hair shafts found on whites. In Africa, lice have adapted to the noncylindrical hair shafts of blacks.

Treatments of head lice abound, recalling the medical adage that if there are many treatments for a condition, it is probably because none of them are really good. Nonprescription medications such as Nix (permethrin insecticide) and Rid (pyrethrin insecticide) are usually the first-choice treatment, but resistance has become common. Other topical preparations containing insecticides such as malathion (Ovide) and the more toxic lindane are also available (lindane is banned in some areas). A single-dose treatment with orally administered ivermectin is occasionally used. A silicone-based product, LiceMD, is effective and nontoxic. The active principle, *dimethicone,* blocks the breathing tubes of the louse. Combing out the nits with fine-toothed louse combs is another treatment option. This is a difficult, time-consuming procedure that has actually led to the appearance of professional removal services in some cities: expensive, but often worth the price to busy parents.

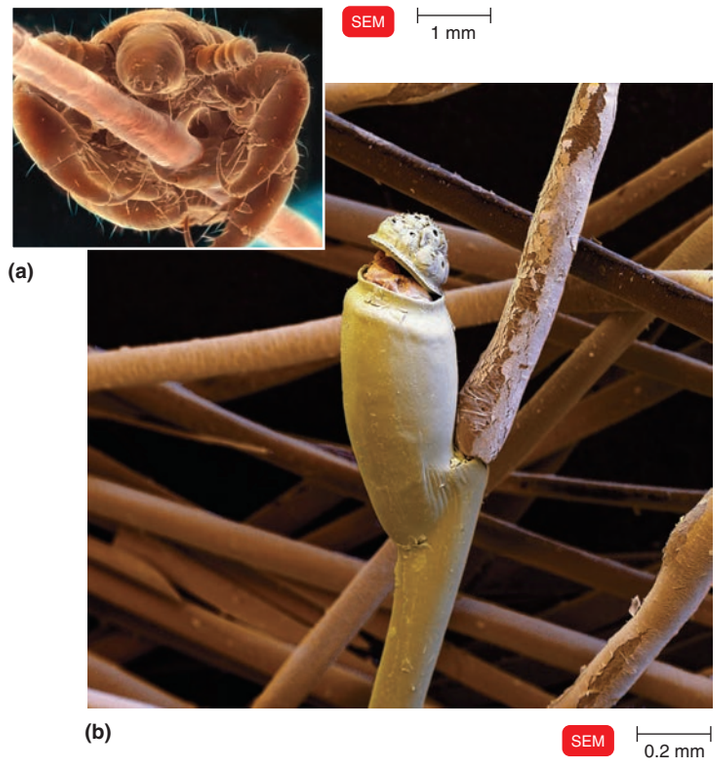
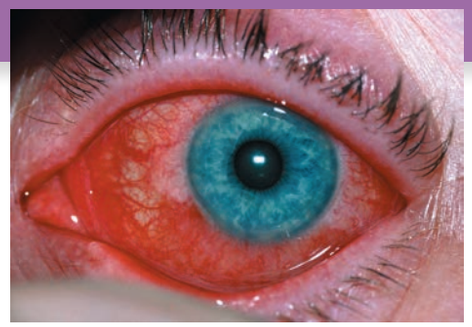


Figure 21.19 Louse and louse egg case. **(a)** Adult louse grasping hair. **(b)** This egg case (nit) contains the nymphal stage of the louse, which is in the process of exiting through the cap (operculum). It does this by gulping air and forcing it out the anus until it pops free, much like a champagne cork.

How is pediculosis transmitted?

DISEASES IN FOCUS 21.4

Microbial Diseases of the Eye



In the morning a 20-year-old man has eye redness with a crust of mucus. The condition resolves with topical antibiotic treatment. Use the table below to provide a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.

Disease	Pathogen	Portal of Entry	Symptoms	Method of Transmission	Treatment
BACTERIAL DISEASES					
Conjunctivitis	*Haemophilus influenzae*	Conjunctiva	Redness	Direct contact; fomites	None
Ophthalmia Neonatorum	*Neisseria gonorrhoeae*	Conjunctiva	Acute infection with much pus formation	Through birth canal	Prevention: tetracycline, erythromycin, or povidone-iodine
Inclusion Conjunctivitis	*Chlamydia trachomatis*	Conjunctiva	Swelling of eyelid; mucus and pus formation	Through birth canal; swimming pools	Tetracycline
Trachoma	*Chlamydia trachomatis*	Conjunctiva	Conjunctivitis	Direct contact; fomites; flies	Azithromycin
VIRAL DISEASES					
Conjunctivitis	Adenoviruses	Conjunctiva	Redness	Direct contact	None
Herpetic Keratitis	Herpes simplex type 1 virus	Conjunctiva; cornea	Keratitis	Direct contact; recurring latent infection	Trifluridine may be effective
PROTOZOAN DISEASE					
***Acanthamoeba* Keratitis**	*Acanthamoeba* spp.	Corneal abrasion; soft contact lenses may prevent removal of ameba by blinking	Keratitis	Contact with fresh water	Topical propamidine isethionate or miconazole; corneal transplant or eye removal surgery may be required

CHECK YOUR UNDERSTANDING

What diseases, if any, are spread by head lice, such as *Pediculus humanus capitis*? **21-8**

Microbial Diseases of the Eye

LEARNING OBJECTIVES

21-9 Define *conjunctivitis.*

21-10 List the causative agent, mode of transmission, and clinical symptoms of these eye infections: ophthalmia neonatorum, inclusion conjunctivitis, trachoma.

21-11 List the causative agent, mode of transmission, and clinical symptoms of these eye infections: herpetic keratitis, *Acanthamoeba* keratitis.

The epithelial cells covering the eye can be considered a continuation of the skin or mucosa. Many microbes can infect the eye, largely through the *conjunctiva,* the mucous membrane that lines the eyelids and covers the outer white surface of the eyeball. It is a transparent layer of living cells replacing the skin. Diseases of the eye are summarized in Diseases in Focus 21.4.

Inflammation of the Eye Membranes: Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva, often called by the common name **red eye,** or **pinkeye.** *Haemophilus influenzae* is the most common bacterial cause; viral conjunctivitis is usually caused by adenoviruses. However, a broad group of bacterial and viral pathogens as well as allergies can also cause this condition.

BIG PICTURE

Fungal Keratitis

Corneal infections are on the rise because of the popularity of extended-wear contact lenses, frequent use of topical antibiotics and steroids, and increasing numbers of cosmetic surgeries. Cases of fungal keratitis are easy to mistake for other diseases and present major treatment challenges.

An Unusual Outbreak

In 2005–2006, epidemiologists noted an outbreak of fungal keratitis with 164 confirmed cases in the United States, 17 in France, 33 in Hong Kong, and 66 in Singapore. Fungal keratitis, a disease that causes inflammation of the cornea that can lead to blindness, is more common in hot, humid climates, but this outbreak occurred in both temperate and tropical climates. Typical cases of fungal keratitis usually occur after eye trauma, but this outbreak was notable in that many of the patients reported no eye injury or surgery prior to infection. Interviews with the patients revealed that most had used the same brand of contact lens solution. An investigation determined that inadequate temperature controls during production, storage, and transport of the solution caused the fungicides in the solution to lose their effectiveness.

Fusarium and Fungal Keratitis

Fusarium spp. are members of the Phylum Ascomycota. These filamentous fungi reside in the soil and are well-known pathogens of plants such as tomatoes and flowering bulbs. They grow in dense mats of hyphae and are characterized by their fusiform conidiospores.

Signs and symptoms of fungal keratitis are a red and painful eye, excessive tearing or discharge, and sensitivity to light. These are similar to other, more common, eye infections, so often the etiologic agent goes undiagnosed. In the 2005–2006 outbreak, typical antibiotics were not effective in treating the infection, an observation that led to the discovery that the infections were caused by fungi rather than bacteria.



A particular brand of contact lens solution was linked to an outbreak of fungal keratitis in 2005–2006.



Petri plate containing left and right contact lenses from a patient with *Fusarium* keratitis. *Source:* CDC.



Lab technician working with *Fusarium* fungal colonies isolated on potato dextrose agar, which had been incubated at 26°C for 5–7 days.

Why Are Fungal Infections So Difficult to Treat?

Several Factors Create Treatment Problems

- *Fusarium* and other fungi form biofilms. Recall that a biofilm is a slimy layer that builds at the interface of a solid surface (in this case, the contact lens) and a liquid (the contact lens solution). *Fusarium* fungi form a dense mat of hyphae on the surface of a contact lens, making it very difficult for antimicrobial drugs to reach all of the fungal cells.
- *Fusarium* spp. are resistant to many drugs. Many antifungal drugs are not effective against these pathogens, and the ones that are effective tend to have high minimal inhibitory concentrations.

Eukaryotic Pathogen Challenges

Because fungi are eukaryotes, just as we are, it is more difficult to find a cellular difference to target than it is for prokaryotic pathogens. Most common antifungal drugs focus on the fungal cell walls or ergosterols in the plasma membrane, which are not found in human plasma membranes. However, these drugs can often have serious side effects. Corneal tissue is very delicate, so drug choices are reduced even further.

Fungal keratitis infections are treated with topical natamycin. The mode of action of this drug is unknown, but it is theorized that the drug works by binding to the ergosterol component of the fungal membrane, thereby preventing vacuole and membrane fusion in the fungus. Natamycin is the only antifungal drug approved for treatment of fungal keratitis.



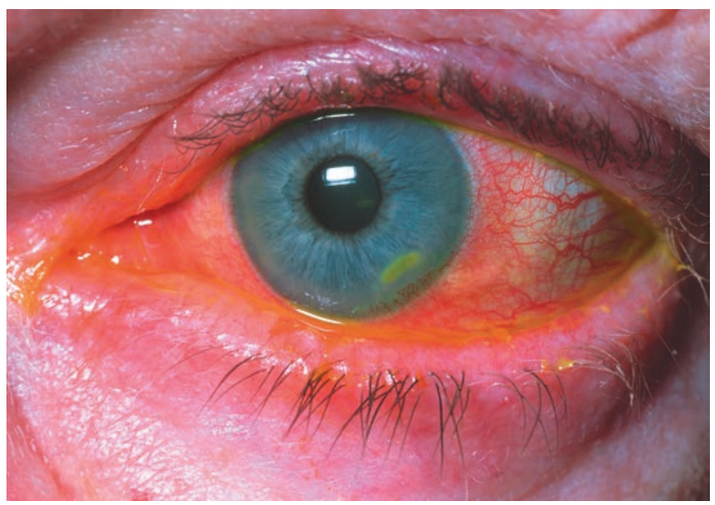
***Fusarium solani* biofilm photographed with a confocal microscope. The biofilm consists of a relatively dense mat of living fungal hyphae.**

CF 5 μm



The fungus *Fusarium solaris,* a cause of fungal keratitis. Conidiospores are produced from the tips of the hyphae.

LM 20 μm



The signs of fungal keritits include a red and painful eye, excessive tearing, and discharge.

KEY CONCEPTS

- Fungi in the Phylum Ascomycota often reproduce by asexual spores called conidia, allowing the fungus to spread. **(See Chapter 12, "Medically Important Fungi," pages 326–328.)**
- When a pathogen forms a biofilm, it is more diffcult for antimicrobial drugs to reach the fungal cells. **(See Chapter 6, "Biofilms," pages 156–157.)**
- Because fungi are eukaryotes, it is more difficult to find a cellular drug target that will not affect our own cells. **(See Chapter 20, "Antifungal Drugs," pages 564–565, and "Tests to Guide Chemotherapy," pages 567–569.)**
- When epidemiologists learned of the increased incidence of fungal keratitis, they used analytical epidemiology to look for similarities among the cases to determine the probable cause. **(See Chapter 14, "Analytical Epidemiology," page 409.)**

The popularity of contact lenses has been accompanied by an increased incidence of infections of the eye. This is especially true of the soft-lens varieties, which are often worn for extended periods. Among the bacterial pathogens that cause conjunctivitis are pseudomonads, which can cause serious eye damage. To prevent infection, contact lens wearers should not use homemade saline solutions, which are a frequent source of infection, and should scrupulously follow the manufacturer's recommendations for cleaning and disinfecting the lenses. The most effective methods for disinfecting contact lenses involve applying heat; lenses that cannot be heated can be disinfected with hydrogen peroxide, which is then neutralized.

Bacterial Diseases of the Eye

The bacterial microorganisms most commonly associated with the eye usually originate from the skin and upper respiratory tract.

Ophthalmia Neonatorum

Ophthalmia neonatorum is a serious form of conjunctivitis caused by *Neisseria gonorrhoeae,* the cause of gonorrhea. Large amounts of pus are formed; if treatment is delayed, ulceration of the cornea will usually result. The disease is acquired as the infant passes through the birth canal, and infection carries a high risk of blindness. Early in the twentieth century, legislation required that the eyes of all newborn infants be treated with a 1% solution of silver nitrate, which proved to be a very effective treatment in preventing this eye infection, which previously accounted for nearly one-quarter of all cases of blindness in the United States. Silver nitrate has been almost entirely replaced by antibiotics because of frequent coinfections by gonococci and sexually transmitted chlamydias, which silver nitrate is not effective against. In parts of the world where the cost of antibiotics is prohibitive, a dilute solution of povidone-iodine has proven effective.

Inclusion Conjunctivitis

Chlamydial conjunctivitis, or **inclusion conjunctivitis,** is quite common today. It is caused by *Chlamydia trachomatis,* a bacterium that grows only as an obligate intracellular parasite. In infants, who acquire it in the birth canal, the condition tends to resolve spontaneously in a few weeks or months, but in rare cases it can lead to scarring of the cornea. Chlamydial conjunctivitis also appears to spread in the unchlorinated waters of swimming pools; in this context, it is called *swimming pool conjunctivitis.* Tetracycline applied as an ophthalmic ointment is an effective treatment.

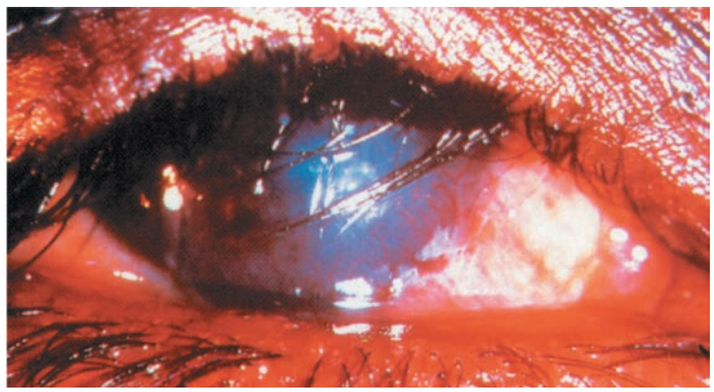
Trachoma

A serious eye infection, and probably the greatest single cause of blindness by an infectious disease, is **trachoma**—an ancient name derived from the Greek word for rough. It is caused by certain serotypes of *Chlamydia trachomatis* but not the same ones that cause genital infections (see pages 755, 757 and 760). In the arid parts of Africa and Asia, almost all children are infected early in their lives. Worldwide, there are probably 500 million active cases and 7 million blinded victims. Trachoma also occurs occasionally in the southwestern United States, especially among Native Americans.

The disease is a conjunctivitis transmitted largely by hand contact or by sharing such personal objects as towels. Flies may also carry the bacteria. Repeated infections cause inflammation (**Figure 21.20a**), leading to *trichiasis,* an in-turning of the eyelashes (Figure 21.20b). Abrasion of the cornea, especially by the eyelashes, eventually causes scarring of the cornea and blindness. Trichiasis can be corrected surgically, a procedure shown in ancient Egyptian papyri. Secondary infections by other bacterial pathogens are also a factor in the disease. Antibiotics to eliminate chlamydia, especially oral azithromycin, are useful in treatment. The disease can be controlled through sanitary practices and health education.



(a) Chronic inflammation of the eyelid



(b) Trichiasis, inturned eyelashes, abrading the cornea

Figure 21.20 Trachoma. **(a)** Repeated infection with *Chlamydia trachoma* causes chronic inflammation. The eyelid has been pulled back to show the inflammatory nodules that are in contact with the cornea. The abrasion caused by this damages the cornea and makes it susceptible to secondary infections. **(b)** In later stages of trachoma, the eyelashes turn inward (trichiasis) as shown here, further abrading the cornea.

Q How is trachoma transmitted?

CHECK YOUR UNDERSTANDING

- What is the common name of inclusion conjunctivitis? **21-9**
- Why have antibiotics almost entirely replaced the less expensive use of silver nitrate for preventing ophthalmia neonatorum? **21-10**

Other Infectious Diseases of the Eye

Microorganisms such as viruses and protozoa can also cause eye diseases. The diseases discussed here are characterized by inflammation of the cornea, which is called *keratitis.* In the United States, keratitis is mostly bacterial in origin; in Africa and Asia, eye infections are mostly caused by fungi, such as *Fusarium* and *Aspergillus.*

For more on fungal keratitis, see the **Big Picture** (on pages 600–601).

Herpetic Keratitis

Herpetic keratitis is caused by the same *herpes simplex type 1 virus* (HSV-1) that causes cold sores and is latent in the trigeminal nerves (see Figure 21.13). The disease is an infection of the cornea, often resulting in deep ulcers, that may be the most common cause of infectious blindness in the United States. The drug trifluridine is often an effective treatment.

Acanthamoeba Keratitis

The first case of ***Acanthamoeba* keratitis** was reported in 1973 in a Texas rancher. Since then, well over 4000 cases have been diagnosed in the United States. This ameba has been found in fresh water, tap water, hot tubs, and soil. Most recent cases have been associated with the wearing of contact lenses, although any cornea damaged by trauma or infection is susceptible. Contributing factors are inadequate, unsanitary, or faulty disinfecting procedures (only heat will reliably kill the cysts), homemade saline solutions, and wearing the contact lenses overnight or while swimming.

In its early stages, the infection consists of only a mild inflammation, but later stages are often accompanied by severe pain. If started early, treatment with propamidine isethionate eye drops and topical neomycin has been successful. Damage is often so severe as to require a corneal transplant or even removal of the eye. Diagnosis is confirmed by the presence of trophozoites and cysts in stained scrapings of the cornea.

CHECK YOUR UNDERSTANDING

- Of the two eye diseases herpetic keratitis and *Acanthamoeba* keratitis, which is the more likely to be caused by an organism actively reproducing in saline solutions for contact lenses? **21-11**

Clinical Case Resolved

P. aeruginosa is able to withstand relatively high levels of chlorine, so eradicating it from swimming pools is difficult. Its ability to produce a biofilm may be a factor in its hardiness. Because the inflatable never completely dries, the bacteria probably grow inside while it is in storage. The bacteria leak out the seams and enter the body through minor abrasions, possibly obtained by contact with the inflatable. The rash patterns are consistent with handling the inflatable. The one patient who had a rash on her legs but had not used the inflatable most likely acquired her rash from the tile.

Pseudomonas dermatitis outbreaks usually occur as a result of low levels of water disinfectant in pools and hot tubs. In this case, the ability of *Pseudomonas* to grow on organic molecules inside the inflatable contributed to the outbreak. Guidelines for disinfecting pool equipment without damaging the equipment are being developed.

581 589 595 597 603

Study Outline

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Introduction (p. 579)

1. The skin is a physical barrier against microorganisms.
2. Moist areas of the skin support larger populations of bacteria than dry areas.

Structure and Function of the Skin (p. 580)

1. The outer portion of the skin (epidermis) contains keratin, a waterproof coating.
2. The inner portion of the skin, the dermis, contains hair follicles, sweat ducts, and oil glands that provide passageways for microorganisms.
3. Sebum and perspiration are secretions of the skin that can inhibit the growth of microorganisms.
4. Sebum and perspiration provide nutrients for some microorganisms.
5. Body cavities are lined with epithelial cells. When these cells secrete mucus, they constitute the mucous membrane.

Normal Microbiota of the Skin (pp. 580–581)

1. Microorganisms that live on skin are resistant to desiccation and high concentrations of salt.
2. Gram-positive cocci predominate on the skin.
3. Washing does not completely remove the normal skin microbiota.

4. Members of the genus *Propionibacterium* metabolize oil from the oil glands and colonize hair follicles.
5. *Malassezia furfur* yeast grows on oily secretions and may be the cause of dandruff.

Microbial Diseases of the Skin (pp. 581–599)

1. Vesicles are small fluid-filled lesions; bullae are vesicles larger than 1 cm; macules are flat, reddened lesions; papules are raised lesions; and pustules are raised lesions containing pus.

Bacterial Diseases of the Skin (pp. 581–590)

2. The majority of skin microbiota consist of coagulase-negative *Staphylococcus epidermidis.*
3. Almost all pathogenic strains of *S. aureus* produce coagulase.
4. Pathogenic *S. aureus* can produce enterotoxins, leukocidins, and exfoliative toxin.
5. Localized infections (sties, pimples, and carbuncles) result from entry of *S. aureus* through openings in the skin.
6. Impetigo is a highly contagious superficial skin infection caused by *S. aureus.*
7. Toxemia occurs when toxins enter the bloodstream; staphylococcal toxemias include scalded skin syndrome and toxic shock syndrome.
8. Streptococci are classified according to their hemolytic enzymes and cell wall antigens.
9. Group A beta-hemolytic streptococci produce a number of virulence factors: M protein, deoxyribonuclease, streptokinases, and hyaluronidase.
10. Invasive group A beta-hemolytic streptococci cause severe and rapid tissue destruction.
11. *Pseudomonas aeruginosa* produces an endotoxin and several exotoxins.
12. Diseases caused by *P. aeruginosa* include otitis externa, respiratory infections, burn infections, and dermatitis.
13. Infections have a characteristic blue-green pus caused by the pigment pyocyanin.
14. *Mycobacterium ulcerans* causes deep-tissue ulceration.
15. *Propionibacterium acnes* can metabolize sebum trapped in hair follicles.
16. Metabolic end-products (fatty acids) cause inflammatory acne.

Viral Diseases of the Skin (pp. 590–595)

17. Papillomaviruses cause skin cells to proliferate and produce a benign growth called a wart or papilloma.
18. Warts are spread by direct contact.
19. Warts may regress spontaneously or be removed chemically or physically.
20. Variola virus causes two types of skin infections: variola major and variola minor.
21. Smallpox is transmitted by the respiratory route, and the virus is moved to the skin via the bloodstream.
22. Smallpox has been eradicated as a result of a vaccination effort by the World Health Organization.
23. Varicella-zoster virus is transmitted by the respiratory route and is localized in skin cells, causing a vesicular rash.
24. Complications of chickenpox include encephalitis and Reye's syndrome.
25. After chickenpox, the virus can remain latent in nerve cells and subsequently activate as shingles.
26. Shingles is characterized by a vesicular rash along the affected cutaneous sensory nerves.
27. The virus can be treated with acyclovir. An attenuated live vaccine is available.
28. Herpes simplex infection of mucosal cells results in cold sores and occasionally encephalitis.
29. The virus remains latent in nerve cells, and cold sores can recur when the virus is activated.
30. HSV-1 is transmitted primarily by oral and respiratory routes.
31. Herpes encephalitis occurs when herpes simplex viruses infect the brain.
32. Acyclovir has proven successful in treating herpes encephalitis.
33. Measles is caused by measles virus and is transmitted by the respiratory route.
34. Vaccination provides effective long-term immunity.
35. After the measles virus has incubated in the upper respiratory tract, macular lesions appear on the skin, and Koplik's spots appear on the oral mucosa.
36. Complications of measles include middle ear infections, pneumonia, encephalitis, and secondary bacterial infections.
37. The rubella virus is transmitted by the respiratory route and causes a red rash and light fever.
38. Congenital rubella syndrome can affect a fetus when a woman contracts rubella during the first trimester of her pregnancy.
39. Vaccination with live rubella virus provides immunity of unknown duration.
40. Human parvovirus B19 causes fifth disease, and HHV-6 causes roseola.
41. Hand-foot-and-mouth disease is an infection in young children caused by several enteroviruses.

Fungal Diseases of the Skin and Nails (pp. 595–597)

42. Fungi that colonize the outer layer of the epidermis cause dermatomycoses.
43. *Microsporum, Trichophyton,* and *Epidermophyton* cause dermatomycoses called ringworm, or tinea.
44. These fungi grow on keratin-containing epidermis, such as hair, skin, and nails.
45. Diagnosis is based on the microscopic examination of skin scrapings or fungal culture.
46. Sporotrichosis results from a soil fungus that penetrates the skin through a wound.
47. The fungi grow and produce subcutaneous nodules along the lymphatic vessels.
48. *Candida albicans* causes infections of mucous membranes and is a common cause of thrush (in oral mucosa) and vaginitis.
49. *C. albicans* is an opportunistic pathogen that may proliferate when the normal bacterial microbiota are suppressed.
50. Topical antifungal chemicals may be used to treat fungal diseases of the skin.

Parasitic Infestation of the Skin (pp. 597–599)

51. Scabies is caused by a mite burrowing and laying eggs in the skin.
52. Pediculosis is an infestation by *Pediculus humanus.*

Microbial Diseases of the Eye (pp. 599–603)

1. The mucous membrane lining the eyelid and covering the eyeball is the conjunctiva.

Inflammation of the Eye Membranes: Conjunctivitis (pp. 599–602)

2. Conjunctivitis is caused by several bacteria and can be transmitted by improperly disinfected contact lenses.

Bacterial Diseases of the Eye (pp. 602–603)

3. Bacterial microbiota of the eye usually originate from the skin and upper respiratory tract.
4. Ophthalmia neonatorum is caused by the transmission of *Neisseria gonorrhoeae* from an infected mother to an infant during its passage through the birth canal.
5. All newborn infants are treated with an antibiotic to prevent *Neisseria* and *Chlamydia* infection.
6. Inclusion conjunctivitis is an infection of the conjunctiva caused by *Chlamydia trachomatis*. It is transmitted to infants during birth and is transmitted in unchlorinated swimming water.
7. In trachoma, which is caused by *C. trachomatis,* scar tissue forms on the cornea.
8. Trachoma is transmitted by hands, fomites, and perhaps flies.

Other Infectious Diseases of the Eye (p. 603)

9. *Fusarium* and *Aspergillus* fungi can infect the eye.
10. Herpetic keratitis causes corneal ulcers. The etiology is HSV-1 that invades the central nervous system and can recur.
11. *Acanthamoeba* protozoa, transmitted via water, can cause a serious form of keratitis.

Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. Discuss the usual mode of entry of bacteria into the skin. Compare bacterial skin infections with infections caused by fungi and viruses with respect to mode of entry.
2. What bacteria are identified by a positive coagulase test? What bacteria are characterized as group A beta-hemolytic?
3. DRAW IT On the figure below, show the sites of the following infections: impetigo, folliculitis, acne, warts, shingles, sporotrichosis, pediculosis.



4. Complete the table of epidemiology below.

Disease	Etiologic Agent	Clinical Symptoms	Mode of Transmission
Acne			
Pimples			
Warts			
Chickenpox			
Hand-foot-and-mouth disease			
Measles			
Rubella			

5. Why do some states require a test for antibodies against rubella for women before issuing a marriage license?
6. Identify the diseases based on the symptoms in the chart below.

Symptoms	Disease
Koplik's spots	
Macular rash	
Vesicular rash	
Small, spotted rash	
Recurrent "blisters" on oral mucosa	
Corneal ulcer and swelling of lymph nodes	

7. What complications can occur from HSV-1 infections?
8. What is in the MMR vaccine?
9. A patient exhibits inflammatory skin lesions that itch intensely. Microscopic examination of skin scrapings reveals an eight-legged arthropod. What is your diagnosis? How is the disease treated? What would you conclude if you saw a six-legged arthropod?
10. NAME IT This anaerobic, gram-positive rod is found on the skin. Infections are often treated with retinoids or benzoyl peroxide.

Multiple Choice

Use the following information to answer questions 1 and 2. A 6-year-old girl was taken to the physician for evaluation of a slowly growing bump on the back of her head. The bump was a raised, scaling lesion 4 cm in diameter. A fungal culture of material from the lesion was positive for a fungus with numerous conidia.

1. The girl's disease was
   a. rubella.
   b. candidiasis.
   c. dermatomycosis.
   d. a cold sore.
   e. none of the above
2. Besides the scalp, this disease can occur on all of the following *except*
   a. feet.
   b. nails.
   c. the groin.
   d. subcutaneous tissue.
   e. The disease can occur on all of these areas.

Use the following information to answer questions 3 and 4. A 12-year-old boy had a fever, rash, headache, sore throat, and cough. He also had a macular rash on his trunk, face, and arms. A throat culture was negative for *Streptococcus pyogenes*.

3. The boy most likely had
   a. streptococcal sore throat.
   b. measles.
   c. rubella.
   d. smallpox.
   e. hand-foot-and-mouth disease.
4. All of the following are complications of this disease *except*
   a. middle ear infections.
   b. pneumonia.
   c. birth defects.
   d. encephalitis.
   e. All are complications of this disease.
5. A patient has conjunctivitis. If you isolated *Pseudomonas* from the patient's mascara, you would most likely conclude all of the following *except* that
   a. the mascara was the source of the infection.
   b. *Pseudomonas* is causing the infection.
   c. *Pseudomonas* has been growing in the mascara.
   d. the mascara was contaminated by the manufacturer.
   e. All of the above are valid conclusions.
6. You microscopically examine scrapings from a case of *Acanthamoeba* keratitis. You expect to see
   a. nothing.
   b. viruses.
   c. gram-positive cocci.
   d. eukaryotic cells.
   e. gram-negative cocci.

Use the following choices to answer questions 7 through 9.

a. *Pseudomonas*
b. *S. aureus*
c. scabies
d. *Sporothrix*
e. virus

7. Nothing is seen in microscopic examination of a scraping from the patient's rash.
8. Microscopic examination of the patient's ulcer reveals 10 μm ovoid cells.
9. Microscopic examination of scrapings from the patient's rash shows gram-negative rods.
10. Which of the following pairs is *mismatched*?
    a. leading cause of blindness—*Chlamydia*
    b. chickenpox—shingles
    c. HSV-1—encephalitis
    d. Buruli ulcer—stomach acid
    e. none of the above

Analysis

1. A laboratory test used to determine the identity of *Staphylococcus aureus* is its growth on mannitol salt agar. The medium contains 7.5% sodium chloride (NaCl). Why is it considered a selective medium for *S. aureus*?
2. Is it necessary to treat a patient for warts? Explain briefly.
3. Analyses of nine conjunctivitis cases provided the data in the table below. How were these infections transmitted? How could they be prevented?

No.	Etiology	Isolated from Eye Cosmetics or Contact Lenses
5	*S. epidermidis*	+
1	*Acanthamoeba*	+
1	*Candida*	+
1	*P. aeruginosa*	+
1	*S. aureus*	+

4. What factors made the eradication of smallpox possible? What other diseases meet these criteria?

Clinical Applications and Evaluation

1. A hospitalized patient recovering from surgery develops an infection that has blue-green pus and a grapelike odor. What is the probable etiology? How might the patient have acquired this infection?
2. A 12-year-old diabetic girl using continuous subcutaneous insulin infusion to manage her diabetes developed a fever (39.4°C), low blood pressure, abdominal pain, and erythroderma. She was supposed to change the needle-insertion site every 3 days after cleaning the skin with an iodine solution. Frequently she did not change the insertion site more often than every 10 days. Blood culture was negative, and abscesses at insertion sites were not cultured. What is the probable cause of her symptoms?
3. A teenaged male with confirmed influenza was hospitalized when he developed respiratory distress. He had a fever, rash, and low blood pressure. *S. aureus* was isolated from his respiratory secretions. Discuss the relationship between his symptoms and the etiological agent.



In the Clinic

You are a nurse in the neonatal intensive care unit, and your newest patient is a 32-week-old infant whose mother had flulike symptoms prior to delivery. The infant required supplemental oxygen for a few hours of life but soon was weaned off oxygen and tolerated her first feeding without difficulty. At 22 hours, you observe a drop in her heart rate, and despite resuscitation efforts, the infant dies. The next morning you receive a microbiology laboratory report that blood cultures drawn just before the infant's death are growing gram-positive rods. **What is the most likely cause of the infant's infection?**

Hint: Read about bacterial causes of meningitis in this chapter.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

22

Microbial Diseases of the Nervous System

Some of the most devastating infectious diseases are those that affect the nervous system, especially the brain and spinal cord. Damage to these areas can lead to deafness, blindness, learning disabilities, paralysis, and death.

Because of the crucial importance of the nervous system, it is strongly protected from accident and infection by bone and other structures. Even pathogens that are circulating in the bloodstream usually can't enter the brain and spinal cord because of the blood–brain barrier (see Figure 22.2). Occasionally, some trauma will disrupt these defenses with serious consequences. The fluid (cerebrospinal fluid) of the central nervous system is especially vulnerable because it lacks many of the defenses found in the blood. Pathogens capable of causing diseases of the nervous system often have special virulence characteristics that enable them to penetrate these defenses. For example, the pathogen can begin replicating in a peripheral nerve and gradually move into the brain and spinal cord. The protozoan *Naegleria fowleri* (red in the photograph) enters the brain from the olfactory nerve in the nose. *Naegleria* meningoencephalitis is described in the Clinical Case in this chapter.

***Naegleria* ameba (red) in human brain tissue.**

Structure and Function of the Nervous System

LEARNING OBJECTIVES

22-1 Define *central nervous system* and *blood–brain barrier.*

22-2 Differentiate meningitis from encephalitis.

The human nervous system is organized into two divisions: the central nervous system and the peripheral nervous system (Figure 22.1). The **central nervous system (CNS)** consists of the brain and the spinal cord. As the control center for the entire body, the CNS picks up sensory information from the environment, interprets the information, and sends impulses that coordinate the body's activities. The **peripheral nervous system (PNS)** consists of all the nerves that branch off from the brain and spinal cord. These peripheral nerves are the lines of communication between the central nervous system, the various parts of the body, and the external environment.

Both the brain and the spinal cord are covered and protected by three continuous membranes called *meninges* (Figure 22.2). These are the outermost *dura mater,* the middle *arachnoid mater,* and the innermost *pia mater.* Between the pia mater and arachnoid membranes is a space called the *subarachnoid space,* in which an adult has 100 to 160 ml of **cerebrospinal fluid (CSF)** circulating. Because CSF has low levels of complement or circulating antibodies and few phagocytic cells, bacteria can multiply in it with few checks.

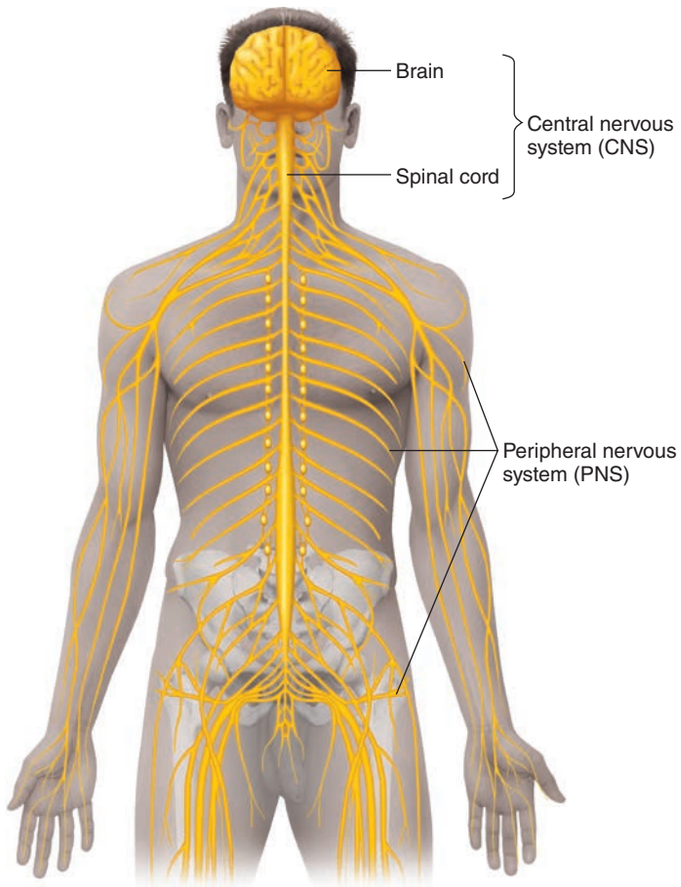


Figure 22.1 The human nervous system. This view shows the central and peripheral nervous systems.

Q Is meningitis an infection of the CNS or the PNS?

Late in the nineteenth century, experiments in which dyes were injected into the body resulted in the staining of all the organs of the body—with the important exception of the brain. Conversely, when the CSF was injected with dyes, only the brain was stained. These remarkable results were the first evidence of an important feature of anatomy: the **blood–brain barrier.** Certain capillaries permit some substances to pass from the blood into the brain but restrict others. These capillaries are less permeable than others within the body and are therefore more selective in passing materials.

Drugs cannot cross the blood–brain barrier unless they are lipid-soluble. (Glucose and many amino acids are not lipid-soluble, but they can cross the barrier because special transport systems exist for them.) The lipid-soluble antibiotic chloramphenicol enters the brain readily. Penicillin is only slightly lipid-soluble; but, if it is taken in very large doses, enough may cross the barrier to be effective. Inflammations of the brain tend to alter the blood–brain barrier in a way that allows antibiotics to cross it when they wouldn't be able to otherwise. Probably the most common routes of CNS invasion are the bloodstream and the lymphatic system (see Chapter 23), when inflammation alters permeability of the blood–brain barrier.

An inflammation of the meninges is called **meningitis.** An inflammation of the brain itself is called **encephalitis.** If both the brain and the meninges are affected, the inflammation is called **meningoencephalitis.**

Clinical Case: Keep Your Head above Water

As her parents look on, EMTs load 9-year-old Patricia Scott into the back of the ambulance. Patricia's mother tells one of the EMTs that 3 days earlier Patricia complained of a severe headache. Over the next 3 days she experienced nausea and vomiting. When normally energetic Patricia became increasingly lethargic, and then unresponsive, Patricia's father called 911.

What could be causing Patricia's sickness? Read on to find out.

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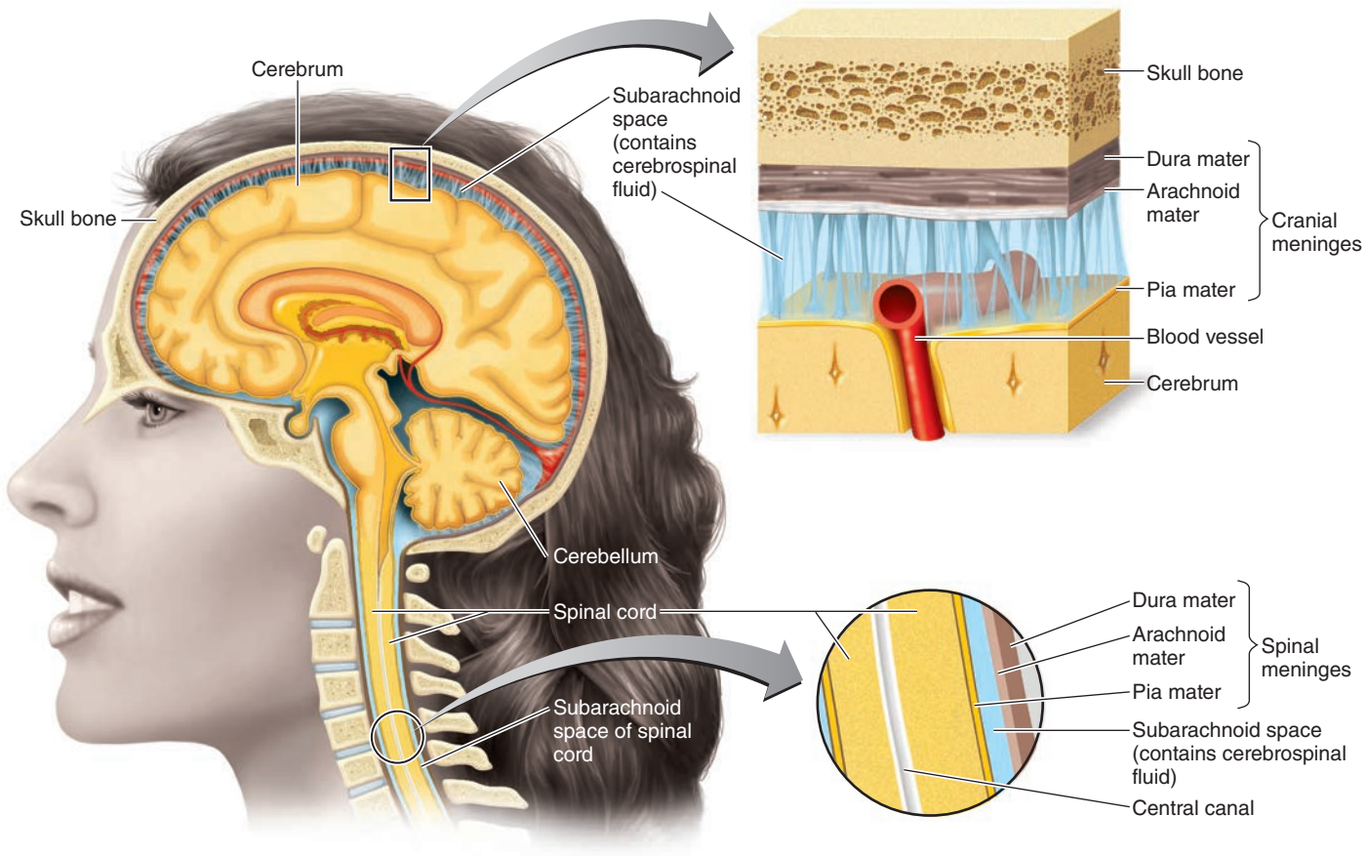


Figure 22.2 The meninges and cerebrospinal fluid. The meninges, whether cranial or spinal, consist of three layers: dura mater, arachnoid mater, and pia mater. Between the arachnoid and the pia mater is the subarachnoid space, in which cerebrospinal fluid circulates. The CSF is vulnerable to contamination by microbes carried in the blood that are able to penetrate the blood–brain barrier at the walls of the blood vessels.

Q If a patient has meningitis, what barriers would need to be crossed to result in encephalitis?

CHECK YOUR UNDERSTANDING

- Why can the antibiotic chloramphenicol readily cross the blood–brain barrier, whereas most other antibiotics cannot? **22-1**
- Encephalitis is an inflammation of what organ or organ structure? **22-2**

Bacterial Diseases of the Nervous System

LEARNING OBJECTIVES

22-3 Discuss the epidemiology of meningitis caused by *Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae,* and *Listeria monocytogenes.*

22-4 Explain how bacterial meningitis is diagnosed and treated.

22-5 Discuss the epidemiology of tetanus, including mode of transmission, etiology, disease symptoms, and preventive measures.

22-6 State the causative agent, symptoms, suspect foods, and treatment for botulism.

22-7 Discuss the epidemiology of leprosy, including mode of transmission, etiology, disease symptoms, and preventive measures.

Microbial infections of the CNS are infrequent but often have serious consequences. In preantibiotic times, they were almost always fatal.

Bacterial Meningitis

The initial symptoms of meningitis are not especially alarming: a triad of fever, headache, and a stiff neck. Nausea and vomiting often follow. Eventually, meningitis may progress to convulsions and coma. The mortality rate varies with the pathogen but is generally high for an infectious disease today. Many people who survive an attack suffer some degree of neurological damage.

Meningitis can be caused by different types of pathogens, including viruses, bacteria, fungi, and protozoa. **Viral meningitis**

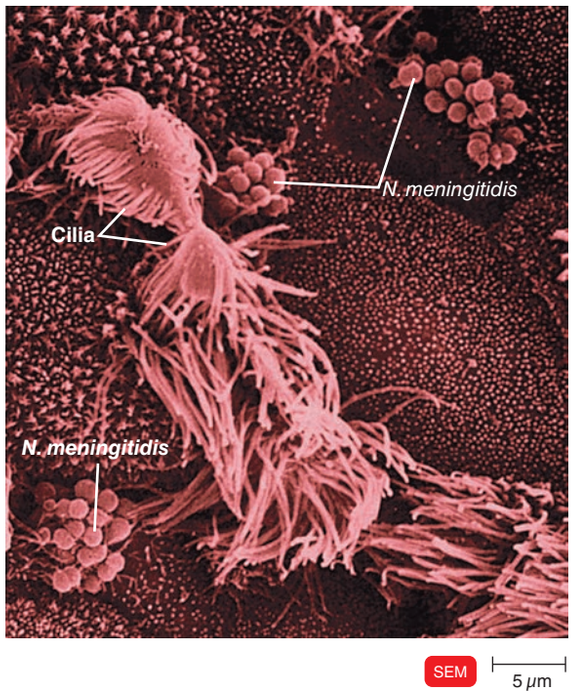


Figure 22.3 *Neisseria* meningitis. This scanning electron micrograph shows *Neisseria meningitidis* in clusters attached to cells on the mucous membrane in the pharynx.

Q What would be the effect if the cilia are inactivated by this infection?

(not to be confused with viral encephalitis, page 624) is probably much more common than bacterial meningitis but tends to be a mild disease. Most cases occur in the summer and fall months and are usually caused by a varied group of viruses termed *enteroviruses* (see Table 13.2, page 365). Enteroviruses grow well in the throat and intestinal tract and are responsible for an assortment of mostly minor diseases. Viral meningitis can also be an occasional complication of viral infections such as mumps, chickenpox, and influenza.

Historically, only three bacterial species have been responsible for most of the meningitis cases and their resulting deaths. Meningitis caused by *Haemophilus influenzae* type B, once responsible for a majority of cases, has been nearly eliminated in the United States since introduction of an effective vaccine. In adult patients, that is, older than 16 years, about 80% of meningitis cases are now caused by *Neisseria meningitidis* and *Streptococcus pneumoniae*. A conjugate vaccine against *S. pneumoniae* is coming into widespread use and is expected to lower its incidence as a cause of meningitis, especially among children. This vaccine may also produce a herd immunity that will benefit the adult population. All three of these pathogens possess a capsule that protects them from phagocytosis as they replicate rapidly in the bloodstream, from which they might enter the cerebrospinal fluid. Death from bacterial meningitis often occurs very quickly, probably from shock and inflammation caused by the release of endotoxins of the gram-negative pathogens or the release of cell wall fragments (peptidoglycans and teichoic acids) from gram-positive bacteria.

Nearly 50 other species of bacteria have been reported to be opportunistic pathogens that occasionally cause meningitis. Especially important are *Listeria monocytogenes,* group B streptococci, staphylococci, and certain gram-negative bacteria.

Haemophilus influenzae Meningitis

Haemophilus influenzae is an aerobic, gram-negative bacterium that is a common member of the normal throat microbiota. Occasionally, however, it enters the bloodstream and causes several invasive diseases. In addition to causing meningitis, it is also frequently a cause of pneumonia (page 690), otitis media (page 679), and epiglottitis. The carbohydrate capsule of the bacterium is important to its pathogenicity, especially those bacteria with capsular antigens of type b. (Strains that lack a capsule are called *nontypable*.) Medically, the bacterium is often referred to by the acronym *Hib*.

It was given the name *Haemophilus influenzae* because the microorganism was erroneously thought to be the causative agent of the influenza pandemics of 1889 and World War I. *H. influenzae* was probably only a secondary invader during those virus-caused pandemics. *Haemophilus* refers to the need the microorganism has for factors in blood for growth (*hemo* = blood; *philus* = loving).

Hib-caused meningitis occurs mostly in children under age 4, especially at about 6 months, when antibody protection provided by the mother weakens. The incidence is decreasing because of the Hib vaccine, which was introduced in 1988. *H. influenzae* meningitis has accounted for most of the cases of reported bacterial meningitis (45%), with a mortality rate of about 6%.

Neisseria meningitidis Meningitis (Meningococcal Meningitis)

Meningococcal meningitis is caused by *Neisseria meningitidis* (the **meningococcus**). This is an aerobic, gram-negative bacterium with a polysaccharide capsule that is important to its virulence. Like Hib and the pneumococcus, it is frequently present in the nose and throat of carriers without causing disease symptoms (**Figure 22.3**). These carriers, up to 40% of the population, are a reservoir of infection. Transmission is by droplet aerosols or direct contact with secretions.

The symptoms of meningococcal meningitis are mostly caused by an endotoxin that is produced very rapidly and is capable of causing death within just a few hours. The most distinguishing feature is a rash that does not fade when pressed. A case of meningococcal meningitis typically begins with a throat infection, leading to bacteremia and eventually meningitis. It usually occurs in children under 2 years. Significant numbers of these children have residual damage, such as deafness.

Death can occur within a few hours after the onset of fever; however, antibiotic therapy has helped reduce the mortality rate to about 9–12%. Without chemotherapy, mortality rates approach 80%.

The meningococcus occurs in six capsular serotypes associated with invasive disease (A, B, C, W-135, X, and Y). The distribution and frequency of these serotypes varies continuously. Local outbreaks are facilitated by modern ease of travel, which often exposes populations to serotypes that are otherwise uncommon in the area. Meningococcal meningitis is a global problem; the World Health Organization (WHO) estimates that about 1.2 million cases and 171,000 deaths occur worldwide annually, with the greatest burden falling on nonindustrialized countries.

The incidence in industrialized countries is sporadic and varies by age, occurring most often in infants who have not yet developed protective antibodies. In arid regions of Africa and Asia, dry air causes the nasal mucous membranes to become less resistant to bacterial invasion. This contributes to widespread epidemics, mostly of serotype A and C. In particular, sub-Saharan Africa, the so-called meningitis belt, regularly experiences devastating outbreaks of serotype A. However, a conjugate vaccine for serogroup A has had encouraging results, leading to hopes that epidemic meningitis might eventually be eliminated from the area.

In the United States, sporadic meningococcal outbreaks occur among college students, presumably as a result of crowding of susceptible populations in dormitories. Before vaccination was introduced in 1982, these outbreaks were a major problem for the U.S. military in recruit barracks. Vaccination is often recommended for students entering college and is required by some institutions.

The three meningococcal serogroups that most commonly circulate and cause disease in the United States are B, C, and Y. The available vaccines target the polysaccharide capsular material of serogroups A, C, Y, and W-135 (sometimes simply referred to as W). Most important, there is no effective vaccine for serogroup B, a disease that still causes high mortality rates, especially in infants. Infants often have a mortality rate as high as 10%, and another 10–20% suffer severe damage, such as loss of hearing and other neurological problems. A vaccine directed at serogroup B has been licensed in Europe, Canada, and Australia but is not routinely used.

The reason for the lack of success in developing a vaccine for serogroup B is that the targeted polysaccharides are not strongly immunogenic, probably because they are too similar to the glycopeptides found on human neural cells. Intensive research has identified noncapsular antigens on these bacteria that are not polysaccharides and that can produce antibodies to kill the pathogen. A vaccine based on this information is still undergoing development and clinical trials; it has been used in a few specific outbreaks.

Streptococcus pneumoniae Meningitis (Pneumococcal Meningitis)

Streptococcus pneumoniae, like *H. influenzae,* is a common inhabitant of the nasopharyngeal region. About 70% of the general population are healthy carriers. The pneumococcus, so called because it is best known as a cause of pneumonia (Chapter 24), is a gram-positive, encapsulated diplococcus. It is the leading cause of bacterial meningitis, now that an effective Hib vaccine is in use. In addition to approximately 6000 cases of meningitis, each year *S. pneumoniae* causes 500,000 cases of pneumonia and millions of cases of painful otitis media (earache). Most of the cases of pneumococcal meningitis occur among children between the ages of 1 month and 4 years. For a bacterial disease, the mortality rate is very high: about 30% in children and 80% in the elderly.

A conjugated vaccine, modeled after the Hib vaccine, has been introduced. It is recommended for infants under the age of 2 (see Table 18.3, page 495). One useful side effect of this vaccine is that it results in about a 6–7% decrease in cases of otitis media. The large number of serotypes of the pneumococcus will make it difficult to develop vaccines against all of them.

A serious problem with meningitis and other diseases caused by the pneumococcus is the increasing appearance of antibiotic-resistant strains.

Diagnosis and Treatment of the Most Common Types of Bacterial Meningitis

A diagnosis of bacterial meningitis requires a sample of cerebrospinal fluid obtained by a spinal tap, or lumbar puncture (**Figure 22.4**). A simple Gram stain is often useful; it will frequently determine the identity of the pathogen with considerable reliability. Cultures are also made from the fluid. For this purpose, prompt and careful handling is required because many of the likely pathogens are very sensitive and won't survive much storage time or even changes in temperature. The most frequently used type of serological tests performed on CSF are latex agglutination tests. Results are available within about 20 minutes. However, a negative result doesn't eliminate the possibility of less common bacterial pathogens or nonbacterial causes.

Bacterial meningitis is life-threatening and develops rapidly. Therefore, prompt treatment of any type of bacterial meningitis is essential, and chemotherapy of suspected cases is usually initiated before identification of the pathogen is complete. Broad-spectrum third-generation cephalosporins are usually the first choice of antibiotics; some experts recommend including vancomycin. As soon as identification is confirmed, or perhaps when antibiotic sensitivity has been determined from cultures, the antibiotic treatment may be changed. Antibiotics are also valuable in protecting patient contacts against the spread of an outbreak.

Listeriosis

Listeria monocytogenes is a gram-positive rod known to cause stillbirth and neurological disease in animals long before it was

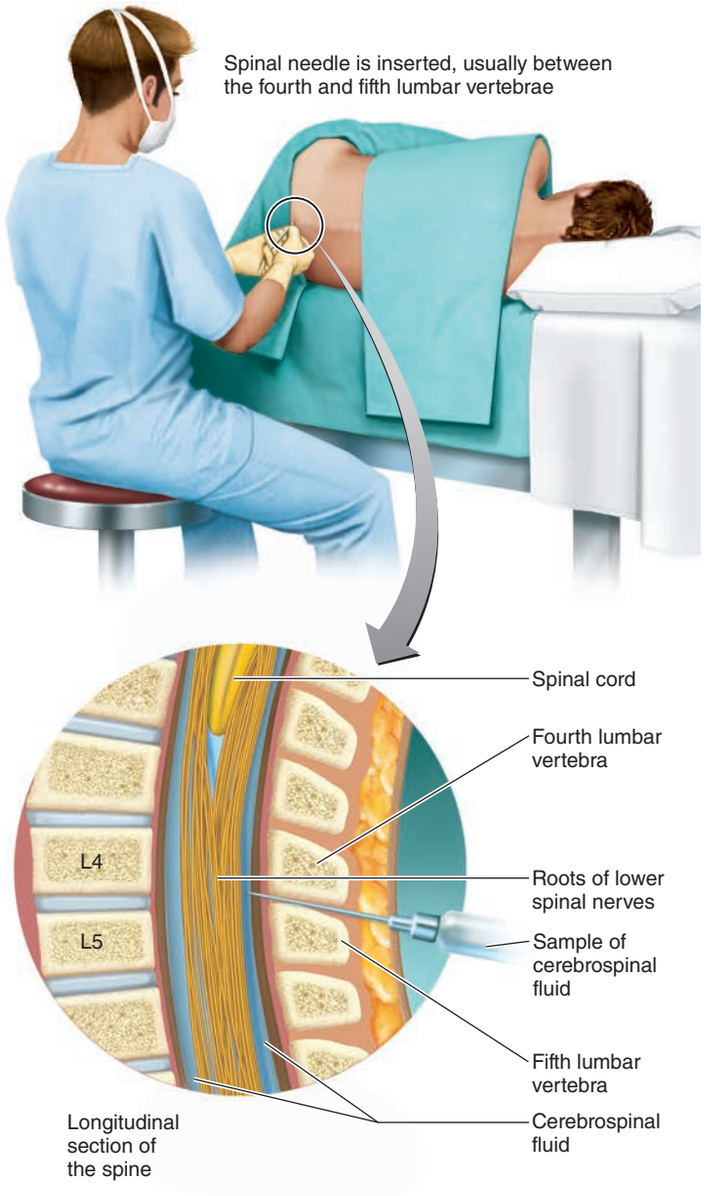


Figure 22.4 Spinal tap (lumbar puncture). Diseases affecting the central nervous system, such as meningitis, often require a spinal tap for diagnosis. A needle is inserted between two vertebrae in the lower spine. A sample of cerebrospinal fluid, which is contained in the subarachnoid space (see Figure 22.2), is withdrawn for laboratory examination.

Q Microscopically, what would you see in CSF from a healthy person? A person with meningococcal meningitis?

recognized as causing human disease. Excreted in animal feces, it is widely distributed in soil and water. The name is derived from the proliferation of monocytes (a type of leukocyte) found in some animals infected by it. In recent years, the disease **listeriosis** has changed from a disease of very limited importance to a major concern for the food industry and health authorities. Since the introduction of the Hib vaccination, listeriosis has become the fourth most common cause of bacterial meningitis.

The disease appears in two basic forms: in infected adults and as an infection of the fetus and newborn. In adult humans, it is usually a mild, often symptomless disease, but the microbe sometimes invades the CNS, causing meningitis. This is most likely to happen to persons whose immune system is compromised, such as persons with cancer, diabetes, or AIDS, or who are taking immunosuppressive medications. Occasionally, *L. monocytogenes* invades the bloodstream and causes a wide range of disease conditions, especially sepsis. Recovering or apparently healthy individuals often shed the pathogen indefinitely in their feces. An important factor in its virulence is that when *L. monocytogenes* is ingested by phagocytic cells, it isn't destroyed; it even proliferates within them, primarily in the liver. It also has the unusual capability of moving directly from one phagocyte to an adjacent one (**Figure 22.5**).

L. monocytogenes is especially dangerous when it infects a pregnant woman. She usually suffers no more than mild, flulike symptoms. The fetus, however, can be infected via the placenta, often resulting in an abortion or stillborn infant. In some cases the disease isn't manifested until a few weeks after birth, usually as meningitis, which can result in significant brain injury or death. The infant mortality rate associated with this type of infection is about 60%.

In human outbreaks, the organism is mostly foodborne. It's frequently isolated from a wide variety of foods; ready-to-eat deli meats and dairy products have been involved in several outbreaks. *L. monocytogenes* is one of the few pathogens capable

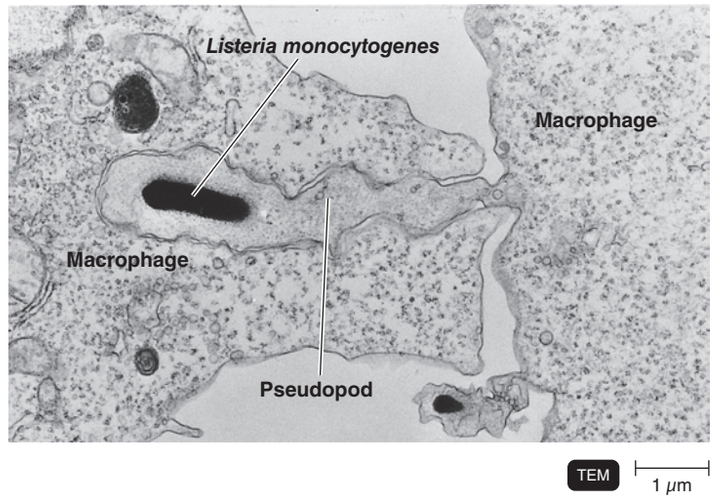


Figure 22.5 Cell-to-cell spread of *Listeria monocytogenes*, the cause of listeriosis. Notice that the bacterium has caused the macrophage on the right, in which it resided, to form a pseudopod that is now engulfed by the macrophage on the left. The pseudopod will soon be pinched off and the microbe transferred to the macrophage on the left.

Q How is listeriosis contracted?

of growth at refrigerator temperatures, which can lead to an increase in its numbers during a food's shelf life. The U.S. Food and Drug Administration (FDA) recently approved the use of a bacteriophage-containing spray capable of killing at least 170 *L. monocytogenes* strains for treating ready-to-eat meats. If it meets with consumer approval, it may be a model for similar sprays to control other foodborne pathogens.

Efforts to improve the methods of detecting *L. monocytogenes* in foods are ongoing. Considerable progress has been made with selective growth media and rapid biochemical tests. However, DNA probes and serological tests using monoclonal antibodies eventually are expected to be the most satisfactory (see Chapter 10). Diagnosis in humans depends on isolating and culturing the pathogen, usually from blood or cerebrospinal fluid. Penicillin G is the antibiotic of choice for treatment.

Microbial causes of meningitis and encephalitis are summarized in Diseases in Focus 22.1.

CHECK YOUR UNDERSTANDING

- Why is meningitis caused by the pathogen *Listeria monocytogenes* frequently associated with ingestion of refrigerated foods? **22-3**
- What body fluid is sampled to diagnose bacterial meningitis? **22-4**

Tetanus

The causative agent of **tetanus,** *Clostridium tetani,* is an obligately anaerobic, endospore-forming, gram-positive rod. It's especially common in soil contaminated with animal fecal wastes.

The symptoms of tetanus are caused by an extremely potent neurotoxin, *tetanospasmin,* that is released upon death and lysis of the growing bacteria (see Chapter 15). It enters the CNS via the peripheral nerves or the blood. The bacteria themselves don't spread from the infection site, and there is no inflammation.

In a muscle's normal operation, a nerve impulse initiates contraction of the muscle. At the same time, an opposing muscle receives a signal to relax so as not to oppose the contraction. The tetanus neurotoxin blocks the relaxation pathway so that both opposing sets of muscles contract, resulting in the characteristic muscle spasms. The muscles of the jaw are affected early in the disease, preventing the mouth from opening, a condition known as *lockjaw.* In extreme cases, spasms of the back muscles cause the head and heels to bow backward, a condition called *opisthotonos* (**Figure 22.6**). Gradually, other skeletal muscles become affected, including those involved in swallowing. Death results from spasms of the respiratory muscles.

Because the microbe is an obligate anaerobe, the wound by which it enters the body must provide anaerobic growth conditions—for example, improperly cleaned deep wounds such as those caused by rusty (and therefore presumably dirt-contaminated) nails. Injecting drug users are at high risk: sanitation during injection is not a priority, and the drugs are often contaminated. However, many cases of tetanus arise from trivial injuries, such as sitting on a tack, that the person considers too minor to bring to the attention of a physician.



Figure 22.6 An advanced case of tetanus. A drawing of a British soldier during the Napoleonic wars. These spasms, known as opisthotonos, can actually result in a fractured spine. (Drawing by Charles Bell of the Royal College of Surgeons, Edinburgh.)

Q What is the name of the toxin that causes opisthotonos?

Effective vaccines for tetanus have been available since the 1940s. But vaccination was not always as common as it is today, where it is part of the standard DTaP (diphtheria, tetanus, and acellular pertussis) childhood vaccine. Currently, about 96% of 6-year-olds in the United States have good immunity, but only about 30% of people age 70 do. The tetanus vaccine is a *toxoid,* an inactivated toxin that stimulates the formation of antibodies that neutralize the toxin produced by the bacteria. A booster is required every 10 years to maintain good immunity, but many people do not obtain these vaccinations. Serological surveys show that at least 50% of the U.S. population does not have adequate protection. In fact, 70% of U.S. tetanus cases occur in individuals over age 50. Some were never immunized at all, and others had lost effective antibody levels over time.

Clinical Case

Once Patricia reaches the emergency department, the attending physician notes her neurological symptoms and orders a lumbar puncture for a bacterial culture and cell count. While performing the lumbar puncture, the physician notes that the cerebrospinal fluid (CSF), which is normally clear in a healthy person, is bloody and cloudy. The lab reports a high white blood cell count, but the bacterial culture is negative.

Based on these findings, what differential diagnosis can the attending physician make?

Even so, immunization has made tetanus in the United States a rare disease—typically, fewer than 50 cases a year. In 1903, 406 people died of fireworks-related tetanus injuries alone. (Fireworks explosions drive soil particles deep into human tissue.) Worldwide, there are an estimated 1 million cases annually; at least half occur in newborns. In many parts of the world, the severed umbilical cords of infants are dressed with materials such as soil, clay, and even cow dung. Estimates are that the mortality rate from tetanus is about 50% in developing areas; in the United States, it is about 25%.

When a wound is severe enough to need a physician's attention, the doctor must decide whether it is necessary to provide protection against tetanus. Usually there isn't enough time to administer the toxoid to produce antibodies and block the progression of the infection, even if given as a booster to a patient who has been immunized. However, temporary immunity can be conferred by *tetanus immune globulin (TIG),* prepared from the antibody-containing serum of immunized humans. (Prior to World War I, long before tetanus toxoid became available, similar preparations of preformed antibodies called *antisera* were used. Made by inoculating horses, antisera were very effective in lowering the incidence of tetanus in injured people.)

A physician's decision for treatment depends largely on the extent of the deep injuries and the immunization history of the patient, who may not be conscious. People with extensive injuries who have previously had three or more doses of toxoid within the past 10 years would be considered protected, requiring no action. For extensive wounds in patients with unknown or low immunity, TIG would be given to provide temporary protection. In addition, the first of a toxoid series would be administered to provide more permanent immunity. When TIG and toxoid are both injected, different sites must be used to prevent the TIG from neutralizing the toxoid. Adults receive a Td (tetanus and diphtheria) vaccine that also boosts immunity to diphtheria. To minimize the production of more toxin, damaged tissue that provides growth conditions for the pathogen should be removed, a procedure called **debridement** (dē-BRĒD-ment) and antibiotics should be administered. However, once the toxin has attached to the nerves, such therapy is of little use.

CHECK YOUR UNDERSTANDING

- Is the tetanus vaccine directed at the bacterium or the toxin produced by the bacterium? **22-5**

Botulism

Botulism, a form of food poisoning, is caused by *Clostridium botulinum,* an obligately anaerobic, endospore-forming gram-positive rod found in soil and many aquatic sediments. Ingesting the endospores usually does no harm, as will be explained shortly. However, in anaerobic environments, such as sealed cans, the microorganism produces an exotoxin. This neurotoxin is highly specific for the synaptic end of the nerve, where it blocks the release of acetylcholine, a chemical necessary for transmitting nerve impulses across synapses.

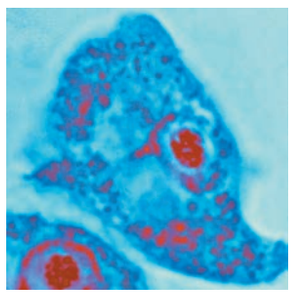
Individuals suffering from botulism undergo a progressive *flaccid paralysis* for 1 to 10 days and may die from respiratory and cardiac failure. Nausea, but no fever, may precede the neurological symptoms. The initial neurological symptoms vary, but nearly all sufferers have double or blurred vision. Other symptoms include difficulty swallowing and general weakness. Incubation time varies, but symptoms typically appear within a day or two. As with tetanus, recovery from the disease does not confer immunity because the toxin is usually not present in amounts large enough to be effectively immunogenic.

Botulism was first described as a clinical disease in the early 1800s, when it was known as the sausage disease (*botulus* is the Latin word for sausage). Blood sausage, the type usually involved, was made by filling a pig stomach with blood and ground meats, tying shut all the openings, boiling it for a short time, and smoking it over a wood fire. The sausage was then stored at room temperature. This attempt at food preservation included most of the requirements for an outbreak of botulism. It killed competing bacteria but allowed the more heat-stable *C. botulinum* endospores to survive, and it provided anaerobic conditions and an incubation period for toxin production.

The botulinal toxin will be destroyed by most ordinary cooking methods that bring the food to a boil. Sausage rarely

Clinical Case

An alert laboratory technician's suspicions are aroused when he sees Patricia's negative bacterial culture. He is certain there must be a reason for pus to be present in Patricia's CSF. The technician prepares a wet mount of the CSF (see the figure) to see whether he can detect a microbial presence in Patricia's CSF.

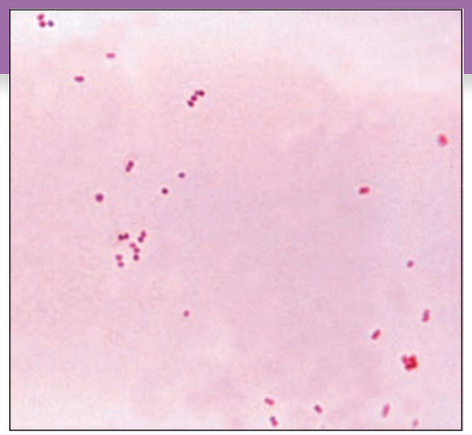


What does the lab technician see in the wet mount of the CSF fluid? How does this affect the physician's diagnosis?

DISEASES IN FOCUS 22.1

Meningitis and Encephalitis

Differential diagnosis is the process of identifying a disease from a list of possible diseases that fit the information derived from examining a patient. A differential diagnosis is important for providing initial treatment and for laboratory testing. For example, a worker in a day-care center in eastern North Dakota becomes ill with fever, rash, headache, and abdominal pain. The patient has a precipitous clinical decline and dies on the first day of hospitalization. A Gram stain of the patient's cerebrospinal fluid is shown in the figure. Use the table below to provide a differential diagnosis of the infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Gram stain of cerebrospinal fluid. LM 6 μm

Disease	Pathogen	Portal of Entry	Method of Transmission	Treatment	Prevention
BACTERIAL DISEASES					
***Haemophilus influenzae* Meningitis**	*H. influenzae*	Respiratory tract	Endogenous infection; aerosols	Cephalosporin	Capsular Hib vaccine
Meningococcal Meningitis	*Neisseria meningitidis*	Respiratory tract	Aerosols	Cephalosporin	Capsular vaccine against serotypes A, C, Y, W-135
Pneumococcal Meningitis	*Streptococcus pneumoniae*	Respiratory tract	Aerosols	Cephalosporin	Polysaccharide vaccine
Listeriosis	*Listeria monocytogenes*	Mouth	Foodborne infection	Penicillin G	Pasteurizing and cooking food
FUNGAL DISEASE					
Cryptococcosis	*Cryptococcus neoformans, C. grubii, C. gattii*	Respiratory tract	Inhaling soil contaminated with spores	Amphotericin B, flucytosine	None
PROTOZOAN DISEASES					
Primary Amebic Meningoencephalitis	*Naegleria fowleri*	Nasal mucosa	Swimming	Amphotericin B	None
Granulomatous Amebic Encephalitis	*Acanthamoeba* spp.; *Balamuthia mandrillaris*	Mucous membranes	Swimming	Amphotericin B	None

causes botulism today, largely because nitrites are added to it. Nitrites prevent *C. botulinum* from growing after the endospores germinate.

Botulinal toxin doesn't form in acidic foods (below pH 4.7). Such acidic foods can therefore be safely preserved without the use of a pressure cooker. There have been cases of botulism from acidic foods that normally would not have supported the growth of the botulism organisms; however, most of these episodes are related to mold growth, which metabolized enough acid to allow *C. botulinum* to begin growing.

Botulinal Types

There are several serological types of the botulinal toxin produced by different strains of the pathogen. These differ considerably in their virulence and other factors.

Type A toxin is probably the most virulent. Deaths have resulted from type A toxin when the food was only tasted but not swallowed. It is even possible to absorb lethal doses through skin breaks while handling laboratory samples. In untreated cases, the mortality rate is 60–70%. The type A endospore is the most heat-resistant of all *C. botulinum* strains. In the United States, it is found mainly in California, Washington, Colorado, Oregon, and New Mexico. The type A organism is usually proteolytic (the breakdown of proteins by clostridia releases amines with unpleasant odors), but obvious spoilage odor is not always apparent in low-protein foods, such as corn and beans (**Figure 22.7**).

Type B toxin is responsible for most European outbreaks of botulism and is the most common type in the eastern United States. The mortality rate in cases without treatment is about 25%. Type B botulism organisms occur in both proteolytic and nonproteolytic strains.



Figure 22.7 Funeral of an Oregon family wiped out by botulism in 1924. The outbreak was caused by home-canned string beans. Altogether there were 12 deaths, but two funerals were held at a different church.

Q Why would such a drastic outcome be unlikely today?

Type E toxin is produced by botulism organisms that are often found in marine or lake sediments. Therefore, outbreaks commonly involve seafood and are especially common in the Pacific Northwest, Alaska, and the Great Lakes area. The endospore of type E botulism is less heat-resistant than that of other strains and is usually destroyed by boiling. Type E is nonproteolytic, so the chance of detecting spoilage by odor in high-protein foods such as fish is minimal. The pathogen is also capable of producing toxin at refrigerator temperatures and requires less strictly anaerobic conditions for growth.

Incidence and Treatment of Botulism

Botulism is not a common disease. Only a few cases are reported each year, but outbreaks from social gatherings or restaurants occasionally involve 20 to 30 cases. About half the cases are type A, and types B and E account about equally for the balance. Alaskan native people probably have the highest rate of botulism in the world, mostly of type E. The problem arises from food preparation methods that reflect a cultural tradition of avoiding the use of scarce fuels for heating or cooking. For example, one food involved in Alaskan outbreaks of botulism is *muktuk*. Muktuk is prepared by slicing the flippers of seals or whales into strips and then drying them for a few days. To tenderize them, they are stored anaerobically in a container of seal oil for several weeks until they approach putrefaction.

Botulism organisms do not seem to be able to compete successfully with the normal intestinal microbiota, so the production of toxin by ingested bacteria almost never causes botulism in adults. However, the intestinal microbiota of infants is not well established, and they may suffer from **infant botulism.** Nearly 100 cases occur in the United States annually, several times more than any other form of botulism. Although infants have ample opportunity to ingest soil and other materials contaminated with the endospores of the organism, many reported cases have been associated with honey. Endospores of *C. botulinum* are recovered with some frequency from honey, and a lethal dose may be as few as 2000 bacteria. The recommendation is not to feed honey to infants under 1 year of age; there is no problem with older children or adults who have normal intestinal microbiota. For treatment of botulism in infants, a special preparation is available, BabyBIG. The acronym BIG represents Botulism Immune Globulin. The immune globulin consists of antibodies to botulism toxin that have been derived from human sources.

Botulism is diagnosed by inoculating mice with samples from patient serum, stool, or vomitus specimens (**Figure 22.8**). Different sets of mice are immunized with type A, B, or E antitoxin. All the mice are then inoculated with the test toxin; if, for example, those protected with type A antitoxin are the only survivors, then the toxin is type A. The toxin in food can similarly be identified by mouse inoculation.

The botulism pathogen can also grow in wounds in a manner similar to that of clostridia causing tetanus or gas gangrene (see Chapter 23). Such episodes of **wound botulism** occur occasionally.

The treatment of botulism relies heavily on supportive care. Recovery requires that the nerve endings regenerate; it therefore proceeds slowly. Extended respiratory assistance may be needed, and some neurological impairment may persist for months. Antibiotics are of almost no use because the toxin is preformed.



Figure 22.8 Diagnosing botulism by identifying botulinal toxin type. To determine whether botulinal toxin is present, mice are injected with the liquid portion of food extracts or cell-free cultures. If the mice die within 72 hours, toxin is present. To determine the specific type of toxin, groups of mice are passively immunized with antisera specific for *C. botulinum* type A, B, or E. If one group of mice receiving a specific antitoxin lives and the other mice die, the type of toxin in the food or culture has been identified.

Q What are the symptoms of botulism?



(a) Tuberculoid (neural) leprosy



(b) Lepromatous (progressive) leprosy

Figure 22.9 Leprosy lesions. **(a)** The depigmented area of skin surrounded by a border of nodules is typical of tuberculoid (neural) leprosy. **(b)** If the immune system fails to control the disease, the result is lepromatous (progressive) leprosy. This severely deformed hand shows the progressive tissue damage to the cooler parts of the body typical of this later stage.

Q Which form of leprosy is more likely to occur in immunosuppressed individuals? Why?

Antitoxins aimed at neutralizing A, B, and E toxins are available and are usually administered together. This trivalent antitoxin will not affect the toxin already attached to the nerve endings and is probably more effective on type E than on types A and B. The antitoxin used in adults is derived from horses and has serious side effects, including *serum sickness* (immune complexes formed by reaction with antigens in the antitoxin) and potential anaphylaxis.

The deadly toxin of botulism (Botox) has therapeutic uses for a number of medical conditions, such as chronic headaches. It is also useful for relieving painful muscle contractions in conditions such as cerebral palsy, Parkinson's disease, and multiple sclerosis. Injections in the area of facial wounds prevent muscle movement during healing and result in more presentable scar formation. It has been approved to control involuntary eyelid twitching (blepharospasm), crossed eyes (strabismus), and even excessive sweating (hyperhidrosis). This latter use, even though it requires expensive twice-yearly injections, prevents armpit sweating and is favored by professional models to help protect expensive designer clothing. However, the most publicized application has been purely cosmetic: periodic local injections of Botox to eliminate forehead wrinkles (worry lines).

CHECK YOUR UNDERSTANDING

The very name *botulism* is derived from the fact that sausage was the most common food causing the disease. Why is sausage now rarely a cause of botulism? **22-6**

Leprosy

Mycobacterium leprae was considered to be the only bacterium that grows in the peripheral nervous system. This distinction, however, is likely also shared with the recently discovered (in 2008) leprosy-causing bacterium *M. lepromatosis,* which is found mostly in Mexico and the Caribbean. *M. leprae* was first isolated and identified around 1870 by Gerhard A. Hansen of Norway; his discovery was one of the first links ever made between a specific bacterium and a disease. **Hansen's disease** is the more formal name for **leprosy;** it is sometimes used to avoid the dreaded name.

These bacteria have an optimum growth temperature of 30°C and show a preference for the outer, cooler portions of the human body. They survive ingestion by macrophages and eventually invade cells of the myelin sheath of the peripheral nervous system, where their presence causes nerve damage from a cell-mediated immune response. It's estimated that *M. leprae* has a very long generation time, about 12 days. *M. leprae* and *M. lepromatosis* have never been grown on artificial media. Armadillos have been found to be a useful way to culture the leprosy bacillus; they have a body temperature of 30–35°C and are often infected in the wild. The animals are now fairly common in warmer states ranging from Texas to Florida. Several people have actually contracted leprosy from contact with armadillos in Texas. Probably the most efficient way of culturing *M. leprae* now is the inoculation of the footpads of nude mice (see Figure 19.12, page 533). The ability to grow the bacteria in an animal is invaluable for evaluating chemotherapeutic drugs.

Leprosy occurs in two main forms (although borderline forms are also recognized) that apparently reflect the effectiveness of the host's cell-mediated immune system. The *tuberculoid (neural) form* is characterized by regions of the skin that have lost sensation and are surrounded by a border of nodules (**Figure 22.9a**). This disease form is roughly the same as *paucibacillary* in the WHO leprosy classification system. Tuberculoid

disease occurs in people with effective immune reactions. Recovery sometimes occurs spontaneously.

In the *lepromatous (progressive) form* of leprosy (which is much the same as *multibacillary* in the WHO system), skin cells are infected, and disfiguring nodules form all over the body. Patients with this type of leprosy have had the least effective cell-mediated immune response, and the disease has progressed from the tuberculoid stage. Mucous membranes of the nose tend to become affected, and a lion-faced appearance is associated with this type of leprosy. Deformation of the hand into a clawed form and considerable necrosis of tissue can also occur (Figure 22.9b). The progression of the disease is unpredictable, and remissions may alternate with rapid deterioration.

The exact means of transfer of the leprosy bacillus is uncertain, but patients with lepromatous leprosy shed large numbers in their nasal secretions and in exudates (oozing matter) of their lesions. Most people probably acquire the infection when secretions containing the pathogen contact their nasal mucosa. However, leprosy is not very contagious and usually is transmitted only between people in fairly intimate and prolonged contact. The time from infection to the appearance of symptoms is usually measured in years, although children can have a much shorter incubation period. Death usually results not from the leprosy itself, but from complications, such as tuberculosis.

Much of the public's fear of leprosy can probably be attributed to biblical and historical references to the disease. In the Middle Ages, people with leprosy were rigidly excluded from normal European society and sometimes even wore bells so that people could avoid them. This isolation might have contributed to the near disappearance of the disease in Europe. But patients with leprosy are no longer kept in isolation, because they can be made noncontagious within a few days by the administration of sulfone drugs. The National Leprosy Hospital in Carville, Louisiana, once housed several hundred patients but was closed in 1999. Most patients today are treated at centers on an outpatient basis.

The number of leprosy cases in the United States is gradually increasing. Currently, about 100 cases are reported each year. Most are imported by infected immigrants from endemic countries; the disease is usually found in tropical climates. Millions of people, most of them in Asia, Africa, and Brazil, suffer from leprosy today, and over half a million new cases are reported each year.

The standard diagnostic test for leprosy is a *skin biopsy sample* taken from the margin of an active lesion. To read this sample reliably, looking for characteristic tissue damage and identifying acid-fast bacilli within nerves, requires an experienced pathologist. Associated procedures, such as the *slit-skin smear,* can be used to enumerate acid-fast bacteria in infected skin. A recent development has been an inexpensive blood test for leprosy that can detect the infection as early as 9 to 12 months, which is in advance of the most damaging clinical symptoms. It has been registered for use in Brazil.

Dapsone (a sulfone drug), rifampin, and clofazimine, a fat-soluble dye, are the principal drugs used for treatment, usually in combination. The WHO treatment regimen for paucibacillary leprosy requires 6 months; for the multibacillary form, treatment is extended to 24 months. A vaccine became commercially available in India in 1998. It is used as an adjunct to chemotherapy. Other vaccines that might be useful in prevention are being tested. One encouraging development is that the Bacillus Calmette-Guérin (BCG) vaccine for tuberculosis (also caused by a *Mycobacterium* species) has been found to be somewhat protective against leprosy.

CHECK YOUR UNDERSTANDING

- Why are nude mice and armadillos important in the study of leprosy? **22-7**

Viral Diseases of the Nervous System

LEARNING OBJECTIVES

22-8 Discuss the epidemiology of poliomyelitis, rabies, and arboviral encephalitis, including mode of transmission, etiology, and disease symptoms.

22-9 Compare the Salk and Sabin polio vaccines.

22-10 Compare the preexposure and postexposure treatments for rabies.

22-11 Explain how arboviral encephalitis can be prevented.

Most viruses affecting the nervous system enter it by circulating in the blood or the lymphatic system. However, some viruses can enter peripheral nerve axons and move along them toward the CNS.

Poliomyelitis

Poliomyelitis (polio) is best known as a cause of paralysis. However, the paralytic form of poliomyelitis probably affects fewer than 1% of those infected with the *poliovirus*. The great majority of cases are asymptomatic or exhibit only mild symptoms, such as headache, sore throat, fever, and nausea.

Polio made its first appearance in the United States in an outbreak in Vermont in the summer of 1894. After that, for decades the country was terrified by summertime epidemics. These annual outbreaks increasingly affected adolescents and young adults, and the number of paralytic cases steadily increased. Many victims died as their respiratory muscles were paralyzed, and thousands of infants and youths were left with their extremities permanently crippled. Later in the twentieth century, development of the iron lung (**Figure 22.10**) kept alive thousands with paralyzed respiratory systems.

Why did this disease seem to appear so suddenly? The answer is paradoxical—probably because of improved sanitation. The primary mode of transmission is ingestion of water

contaminated with feces containing the virus. Improved sanitation delayed exposure to polioviruses in feces until after the protection provided by maternal antibodies had waned. At one time, exposure to the poliovirus was frequent (and is still so today in parts of the world with poor sanitation). Infants were usually exposed to poliovirus while still protected by maternal antibodies. The result was usually an asymptomatic case of the disease and a lifelong immunity. When infection is delayed until adolescence or early adulthood, the paralytic form of the disease appears more frequently.

During the 1980s, many middle-aged adults who had had polio as children began showing a muscle weakness now called *postpolio syndrome.* It may be that nerve cells that had survived polio originally begin to die. Fortunately, the disease progresses extremely slowly.

Because the infection begins when the virus is ingested, its primary areas of multiplication are the throat and small intestine. This accounts for the initial sore throat and nausea. Next, the virus invades the tonsils and the lymph nodes of the neck and ileum (the terminal portion of the small intestine). From the lymph nodes, the virus enters the blood, resulting in *viremia.* In most cases the viremia is only transient, the infection does not progress past the lymphatic system, and clinical disease does not result. If the viremia persists, however, the virus eventually penetrates the capillary walls and enters the CNS. Once in the CNS, the virus displays a high affinity for nerve cells, particularly motor nerve cells in the upper spinal cord. The virus does not infect the peripheral nerves or the muscles. As the virus multiplies within the cytoplasm of the motor nerve cells, the cells die, and paralysis results. Death can result from respiratory failure.

Diagnosis

Polio is usually diagnosed by isolating the virus from feces and throat secretions. Cell cultures can be inoculated, and cytopathic effects on the cells can be observed (see Table 15.4, page 432).

Vaccines

There are three different serotypes of the poliovirus: types 1, 2, and 3. Immunity must be provided for all three.

Two different vaccine types are available. In 1955, the *Salk vaccine* (named after Jonas Salk, its developer) was introduced. It consists of viruses of all three types that have been inactivated (killed) by treatment with formalin. Vaccines of this types, called *inactivated polio vaccines (IPV),* require a series of injections. A version with enhanced potency was introduced in 1988.

The other vaccine type, introduced in 1963, contains living, attenuated (weakened) strains of the virus in a suspension that is ingested. This *Sabin vaccine,* named after its developer (Albert Sabin), is more commonly called *oral polio vaccine (OPV).* It usually contains the three types of polio virus (trivalent, *tOPV*). It is less expensive to manufacture and is simpler to administer because it does not require the trained personnel and equipment needed for safe, sterile injections. This vaccine mimics an actual infection and induces excellent, and probably life-long, immunity, although its use is precluded in immunodeficient individuals. The live virus is also shed by the recipient and has the effect of immunizing others within the community. However, this shedding can represent a serious disadvantage—the attenuated strains of the disease occasionally revert to virulence and cause the disease. The incidence of this varies by region but is usually about 1 case per 750,000 recipients.

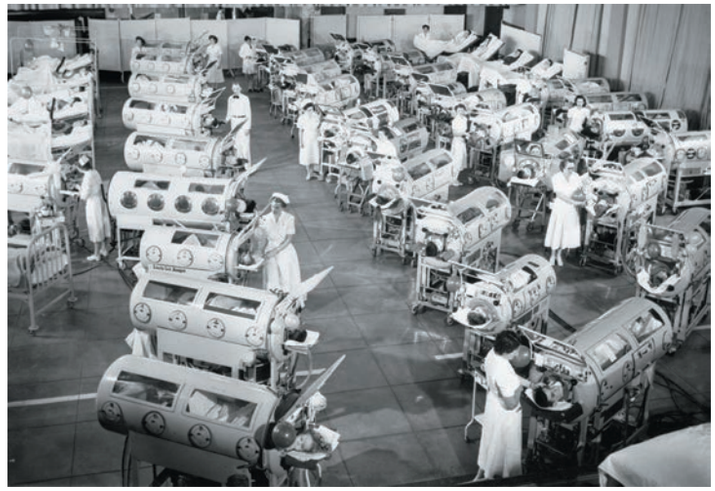


Figure 22.10 Polio patients in iron lungs. Many polio patients were able to breathe only with these mechanical aids. Some 6–8 survivors from these polio epidemics still use these machines, at least part of the time. Others are able to use portable respiratory aids.

Q What percentage of polio cases resulted in paralysis?

The history of polio vaccination in the United States began with the use of the Salk IPV, which was the first available. When OPV was licensed in 1963, its advantages, especially in administration, led to near-universal adoption. Eventually, however, high rates of vaccination led to the disappearance of polio—with the exception of a few cases every year that were caused by the vaccine-derived virus (**Figure 22.11**). In 2000, the United States therefore changed the recommendation from OPV back to IPV.

Research into polio vaccines continues, especially for use in less-developed areas. There is some prospect that IPV might be made less expensive, although with slightly lower effectiveness, by administration of only one-fifth of the standard dose. This dose is administered into the skin rather than the muscle by means of an investigational needle-free device. Also, there have been successful trials, in certain areas, of a more immunogenic version of OPV that consists of only type 1, or types 1 and 3, of the poliovirus. This might allow extended use of OPV.

Epidemiology and Eradication Efforts

In the epidemiology of the poliovirus, naturally occurring, *wild-type (WPV)* virus is distinguished from *vaccine-derived* virus

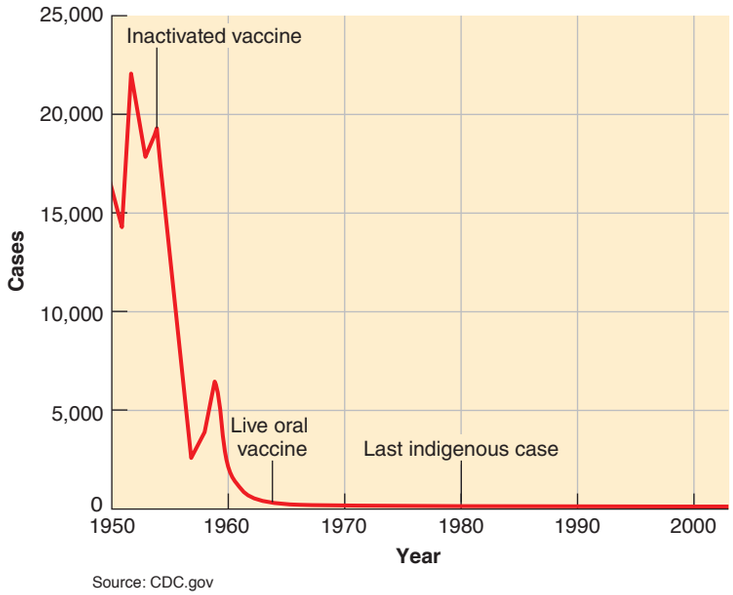


Figure 22.11 U.S. annual incidence of poliomyelitis. Polio from wild-type viruses has been nearly eliminated in the developed world. A global campaign to eradicate the disease was launched in 1988. Whether it can ever be eradicated completely in less-developed parts of the world is becoming questionable.

Data source: CDC

Q Why is it possible to eradicate polio but not tetanus?

(*VDPV*). VDPV is an attenuated vaccine virus that has reverted to virulence and is in circulation.

The WHO launched a campaign in 1988 to eradicate polio by 2000. The vaccine used was tOPV. Although the goal of eradication was not met, great gains were made, and by 2000 the number of case reports had fallen by 99%. Also encouraging was the extinction of WPV 2 poliovirus—indicating that eradication might be possible. However, for various reasons persistent reservoirs of WPV remain in some areas, notably Pakistan, India, Afganistan, and Nigeria. An important factor has been the relative ineffectiveness of the tOPV in areas of poor sanitation and pervasive diarrhea. Undernourished children may have a poor response to the vaccine. This has led to continuing circulation of WPV types 1 and 3, which are introduced into areas where the population has insufficient immunity. An additional problem has been the emergence of VDPV into circulation, causing paralytic polio. It is becoming clear that once WPV has been eradicated, it will be necessary to discontinue use of OPV. Even now, most countries that are able to afford IPV and have the infrastructure to distribute it use IPV exclusively.

CHECK YOUR UNDERSTANDING

- Why is paralytic polio more likely to occur than a mild or asymptomatic infection in areas with high standards of sanitation? **22-8**
- Why is the Sabin oral polio vaccine more effective than the injected Salk polio vaccine? **22-9**

Rabies

Rabies (the word is from the Latin for rage or madness) is a disease that almost always results in fatal encephalitis. The causative agent is the *rabies virus,* a member of the genus *Lyssavirus* having a characteristic bullet shape (see Figure 13.18a and discussion on page 378). Lyssaviruses (*lyssa,* from the Greek for frenzy) are single-stranded RNA viruses with no proofreading capability, and mutant strains develop rapidly. Worldwide, humans usually are infected with the rabies virus in saliva from the bite of an infected animal—especially dogs. On rare occasions, the virus can be transmitted through fresh skin abrasions and may cross the mucous membranes of the nose, mouth, and even eyes. The virus proliferates in the PNS and moves, fatally, toward the CNS (**Figure 22.12**). In the United States, the most common cause of rabies is a variant of the virus found in silver-haired bats. (Domestic animals have a high rate of vaccination.) Because deaths from rabies are frequently misdiagnosed, several cases of rabies have been traced to transplanted body tissues, especially corneas.

Rabies is unique in that the incubation period is usually long enough to allow immunity to develop from postexposure vaccination. The natural immune response is ineffective because the viruses are introduced into the wound in numbers too low to provoke it; also, they do not travel through the bloodstream or lymphatic system, where the immune system could best respond. Initially, the virus multiplies in skeletal muscle and connective tissue, where it remains localized for periods ranging from days

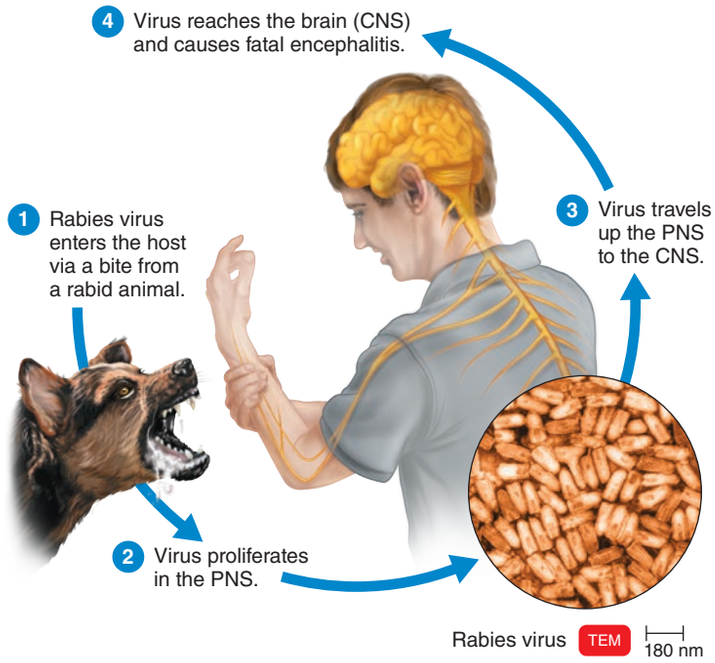


Figure 22.12 Pathology of rabies infection.

Q What is the postexposure treatment for rabies?

to months. Then it enters a motor neuron and travels, at the rate of 15 to 100 mm per day, along peripheral nerves to the CNS, where it causes encephalitis. In some extreme cases, incubation periods of as long as 6 years have been reported, but the average is 30 to 50 days. Bites in areas rich in nerve fibers, such as the hands and face, are especially dangerous, and the resulting incubation period tends to be short.

Once the virus enters the peripheral nerves, it isn't accessible to the immune system until cells of the CNS begin to be destroyed, which triggers a belated and ineffective immune response.

Preliminary symptoms are mild and varied, resembling several common infections. When the CNS becomes involved, the patient tends to alternate between periods of agitation and intervals of calm. At this time, a frequent symptom is spasms of the muscles of the mouth and pharynx that occur when the patient feels air drafts or swallows liquids. In fact, even the mere sight or thought of water can set off the spasms—thus the common name *hydrophobia* (fear of water). The final stages of the disease result from extensive damage to the nerve cells of the brain and the spinal cord.

Animals with **furious (classical) rabies** are at first restless, then become highly excitable and snap at anything within reach. The biting behavior is essential to maintaining the virus in the animal population. Humans also exhibit similar symptoms of rabies, even biting others. When paralysis sets in, the flow of saliva increases as swallowing becomes difficult, and nervous control is progressively lost. The disease is almost always fatal within a few days.

Some animals suffer from **paralytic (dumb** or **numb) rabies,** in which there is only minimal excitability. This form is especially common in cats. The animal remains relatively quiet and even unaware of its surroundings, but it might snap irritably if handled. A similar manifestation of rabies occurs in humans and is often misdiagnosed as Guillain-Barré syndrome, a form of paralysis that is usually transient but sometimes fatal, or other neurological conditions. There is some speculation that the two forms of the disease may be caused by slightly different forms of the virus.

Diagnosis

Rabies is usually diagnosed in the laboratory by detection of the viral antigen using the **direct fluorescent-antibody (DFA) test,** which is nearly 100% sensitive and highly specific. These tests can be done on saliva samples, blood, CSF, and skin; postmortem samples are usually taken from the brain. For less-developed parts of the world, the CDC has recently developed a **rapid immunohistochemical test (RIT).** It requires only the use of an ordinary light microscope and has a sensitivity and specificity equivalent to the standard DFA test.

Prevention of Rabies

Only high-risk individuals, such as laboratory workers, animal control professionals, and veterinarians, are routinely vaccinated against rabies before known exposure. If a person is bitten, the wound should be thoroughly washed with soap and water. If the animal is positive for rabies, the person must undergo **postexposure prophylaxis (PEP)**—meaning a series of antirabies vaccine and immune globulin injections. Another indication for antirabies treatment is any unprovoked bite by a skunk, bat, fox, coyote, bobcat, or raccoon not available for examination. Treatment after a dog or cat bite, if the animal cannot be found, is determined by the prevalence of rabies in the area. The bite of a bat may not be perceptible and may be impossible to rule out in cases where the bat had access to sleeping persons or small children. Therefore, the CDC recommends PEP after any significant encounter with a bat—unless the bat can be tested and shown to be negative for rabies.

The original Pasteur treatment, in which the virus was attenuated by drying in the dissected spinal cords of rabies-infected rabbits, has long been replaced by **human diploid cell vaccine (HDCV),** or chick embryo–grown vaccines. These vaccines are administered in a series of four injections at intervals during a 14-day period. Passive immunization is provided simultaneously by injecting **human rabies immune globulin (RIG)** that has been harvested from people who are immunized against rabies.

Treatment of Rabies

Once the symptoms of rabies appear, there is very little in the way of effective treatment—only a handful of survivors have been reported. Most of these survivors had received PEP before the appearance of symptoms. There have been only a couple of cases of survival of a patient who had not received PEP. The primary treatment, which succeeds in a minority of cases, is to induce an extended coma to minimize excitability while administering antiviral drugs. This procedure was first used in the case of a Wisconsin girl bitten by a rabid cat and has come to be called the Milwaukee protocol.

Distribution of Rabies

Rabies occurs all over the world, mostly a result of dog bites. Vaccination of pets is prohibitively expensive in most of Africa, Latin America, and Asia. In these areas, tens of thousands of deaths by rabies occur annually. In the United States, the vaccination of pets is nearly universal, but rabies is widespread among wildlife, predominantly bats, skunks, foxes, and raccoons, although it is also found in domesticated animals (**Figure 22.13**). As many as 40,000 people are administered postexposure rabies vaccine each year, often as a precaution when the rabies status of the biting animal cannot be determined. Rabies is almost never found in squirrels, rabbits, rats, or mice. The disease has long been endemic in vampire bats of South America. In Europe and North America, there are ongoing experiments to immunize wild animals with live rabies vaccine produced in genetically modified vaccinia viruses that are added to food left for the animals to find. Bait has been used in the United States, especially in Texas, to prevent the

BIG PICTURE

Neglected Tropical Diseases

Neglected Tropical Diseases (NTDs) are a group of 16 diseases contracted by more than a billion people per year.

A Different Kind of Public Health Campaign

Traditionally, public health campaigns target the largest health threats one disease at a time. An unfortunate consequence of this approach is that certain serious infections with lower incidence rates never meet the criteria for major health campaigns. Thus, awareness, prevention, and treatment efforts may fall through the cracks.

Historically, this was the case for 16 infections now known as Neglected Tropical Diseases (NTDs). They disproportionately infect the poorest people living in the least developed areas. NTDs cause a wide variety of maladies, including blindness (trachoma, onchocerciasis); disfigurement (leprosy, lymphatic filariasis, Buruli ulcer); heart problems (Chagas' disease); liver or lung disease (schistosomiasis, fascioliasis, leishmaniasis, echinococcosis); bone, joint, or other movement-related disabilities (yaws, dengue, dracunculiasis); malaise, malnutrition, and cognitive impairment (soil-transmitted helminthiasis); and neurological damage (rabies, cysticercosis, and African trypanosomiasis). Taken as a group, NTDs impact over a billion people annually, with over half a million deaths, according to the Centers for Disease Control and Prevention (CDC).

Despite the wide variance in causes and effects, management strategies for NTDs are frequently similar (see the table). Simultaneous infection with more than one NTD is also common, making a group-management approach a good option for the public health response.

In 2012, the World Health Organization (WHO) issued a declaration that set NTD reduction targets for the year 2020 and outlined ways to attain the goals. Over a dozen major organizations joined forces. Main approaches include new and intensified disease management; zoonotic disease management; preventive chemotherapy; vector control and pesticide management; and improvement of sanitation and drinking water safety.



Adult male and female *Schistosoma*, parasitic worms that infect almost 210 million people worldwide

Infection Type	Disease	Management Strategies
PROTOZOAN		
	African trypanosomiasis	Vector (tsetse fly) control, preventive chemotherapy, intensified disease management, veterinary public health
	Chagas' disease	Vector (triatoma) control, intensified disease management
	Leishmaniasis	Vector (sandfly) control, preventive chemotherapy, intensified disease management
HELMINTHIC		
	Cysticercosis	Veterinary public health, improved sanitation and hygiene
	Dracunculiasis (Guinea worm disease)	Vector (copepods) control, improved hygiene and sanitation
	Echinococcosis	Veterinary public health
	Fascioliasis (foodborne trematodiases)	Veterinary public health, preventive chemotherapy
	Lymphatic filariasis (elephantiasis)	Vector (mosquito) control, preventive chemotherapy, intensified disease management
	Onchocerciasis (river blindness)	Vector (black fly) control, preventive chemotherapy
	Schistosomiasis (soil-transmitted intestinal worms)	Preventive chemotherapy, improved hygiene and sanitation
BACTERIAL		
	Trachoma	Vector (fly) control, annual preventive deworming drugs, improved sanitation and hygiene
	Leprosy (Hansen's disease)	Preventive chemotherapy, intensified disease management
	Buruli ulcer	Vector control (if vector is discovered); preventive chemotherapy, intensified disease management, improved sanitation and hygiene
VIRAL		
	Yaws (endemic treponematosis)	Improved hygiene
	Dengue	Vector control
	Rabies	Veterinary public health

A Few Strategies Can Greatly Reduce Incidence of Neglected Tropical Diseases

By 2020, WHO hopes to eradicate dracunculiasis and eliminate lymphatic filariasis, leprosy, trachoma, and African trypanosomiasis. Efforts to reduce NTDs include the following.

Preventive Chemotherapy

Pharmaceutical firms donate medication and share technology and data to develop new treatments. The World Bank funds initiatives to provide treatments. Preventive medicines for multiple NTDs are packaged and priced at less than $1 per person. Teachers receive training to administer deworming tablets to students. These efforts have confined the transmission of dracunculiasis.

Innovative, Intensified Disease Management

Most people infected with NTDs live in remote areas, so aid groups host community events where people can receive vaccines, vitamins, and drugs outside the clinical setting. Grants from organizations such as the Bill and Melinda Gates Foundation fund development of portable testing devices, allowing for rapid diagnosis and immediate treatment.

Veterinary Care

Veterinary care is expensive, and therefore rare, in developing nations. Treating pets, cattle, and pigs for parasites and bacterial and viral diseases helps break transmission to humans of zoonotic diseases such as rabies, cysticercosis, echinococcosis, foodborne trematodiases, and African trypanosomiasis.

Vector Control

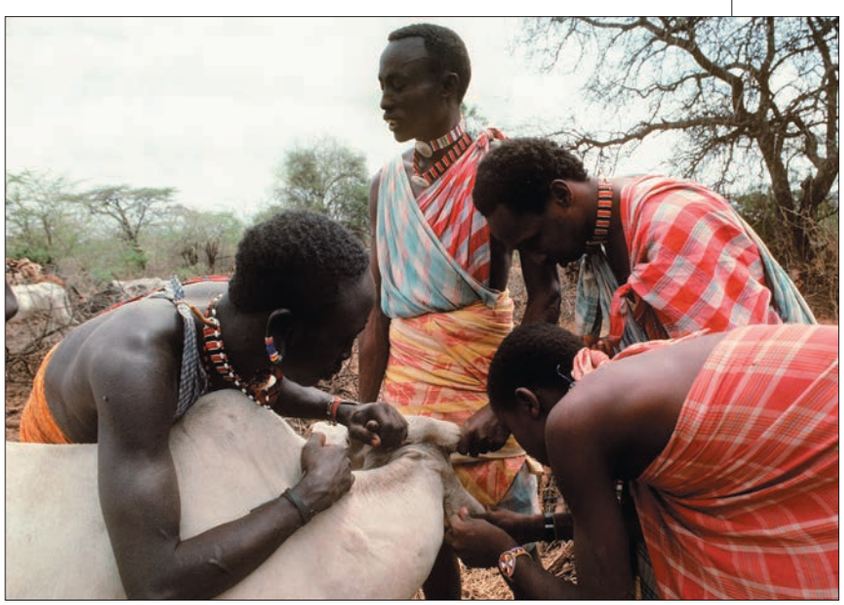
Safe use of pesticides for vector control reduces incidence of African trypanosomiasis, Chagas' disease, leishmaniasis, dengue, dracunculiasis, lymphatic filariasis, and trachoma.

Improved Sanitation and Hygiene Services

Safe drinking water and improved sanitation systems can reduce prevalence of many diseases, including dracunculiasis, schistosomiasis, trachoma, Buruli ulcer, and yaws.



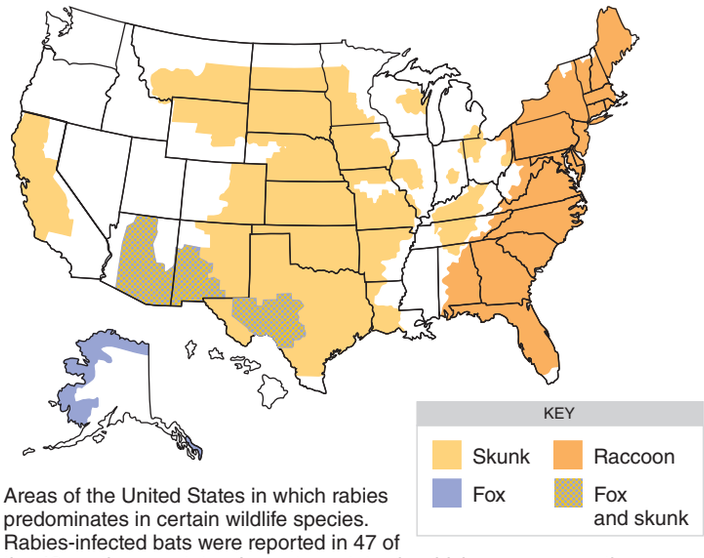
Access to clean water allows daily hand and face washing, which can reduce the transmission of many diseases.



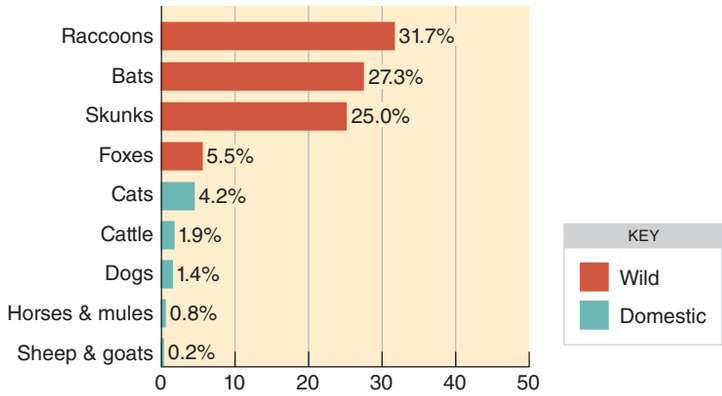
Kenyan Masai take a blood sample from cattle to check for trypanosomes.

KEY CONCEPTS

- Vectors are animals that carry diseases to humans. **(See Chapter 12, "Arthropods as Vectors," pages 351–353, and Chapter 14, "Transmission of Disease," pages 399–402.)**
- Over half the world's population is infected with eukaryotic pathogens, such as protozoans and worms. **(See Chapter 12, "Medically Important Protozoa," pages 338–342, and "Helminths," pages 343–351.)**
- Epidemiologists study patterns in transmission and distribution in order to develop infection control strategies. **(See Chapter 14, "Epidemiology," pages 407–412.)**
- Pet vaccination is prohibitively expensive in most of Africa, Asia, and Latin America, where rabies deaths are much more common. **(See Chapter 22, "Rabies," pages 620–624.)**



Areas of the United States in which rabies predominates in certain wildlife species. Rabies-infected bats were reported in 47 of the 48 contiguous states. In eastern states in which raccoons are the predominant rabies-infected animal, many cases were also reported in foxes and skunks.



Rabies cases in various wild and domestic animals in the United States. Rabies in domestic animals such as dogs and cats is uncommon because of high vaccination rates. Raccoons, skunks, and bats are the animals most likely to be infected with rabies. Most human cases are caused by bat bites. Worldwide, most human cases are caused by dog bites.

Figure 22.13 Reported cases of rabies in animals. Color-shaded areas identify regions in which certain wildlife species are the predominant carrier of rabies. In eastern states in which raccoons are the predominant rabies-infected animal, many cases were also reported in foxes and skunks. Rabies-infected bats were reported in 47 of the 48 contiguous states. Rabies in foxes include different species in different geographical areas.
Source: CDC 2013.

Q What is the primary reservoir for the rabies virus in your area?

reintroduction of rabies from Mexico. These campaigns have been highly successful in Europe, and several countries have been declared free of rabies as a result.

In the United States, 7000 to 8000 cases of rabies are diagnosed in animals each year, but in recent years, only one to six cases have been diagnosed in humans annually (see the Clinical Focus box on the facing page). In developing nations, rabies has a much higher incidence. See pages 622–623 for the **Big Picture** on neglected tropical diseases for more information.

Related *Lyssavirus* Encephalitis

In recent years a few fatal cases of encephalitis that are clinically indistinguishable from classical rabies have occurred in Australia and Scotland—countries considered free of rabies. These cases were found to be caused by genotypes of the genus *Lyssavirus* (see page 378) that are closely related to classical rabies virus: the *Australian bat lyssavirus (ABLV)* and the *European bat lyssavirus (EBLV).**

Classic rabies is caused by one of 11 known genotypes of the genus *Lyssavirus* and is widespread worldwide. Other, nonrabies, lyssaviruses causing encephalitis are indigenous to Europe, Australia, Africa, and Philippines, most commonly in bats. Different species of bats are infected with distinct variants of the rabies virus.

CHECK YOUR UNDERSTANDING

Why is postexposure vaccination for rabies a practical option? **22-10**

Arboviral Encephalitis

Encephalitis caused by mosquito-borne viruses (called arboviruses) is rather common in the United States. (*Arbovirus* is short for *ar*thropod-*bo*rne virus. This terminology represents a functional grouping; it is not a formal taxonomic term.) The incidence of disease increases in the summer months, coinciding with the proliferation of adult mosquitoes. *Sentinel animals,* such as caged chickens, are tested periodically for antibodies to arboviruses. This gives health officials information on the incidence and types of viruses in their area.

A number of clinical types of arboviral encephalitis have been identified; all can cause symptoms ranging from subclinical to severe, including rapid death. Active cases of these diseases are characterized by chills, headache, and fever. As the disease progresses, mental confusion and coma occur. Survivors may suffer from permanent neurological problems.

Horses as well as humans are frequently affected by these viruses; thus, there are strains causing *eastern equine encephalitis (EEE)* and *western equine encephalitis (WEE).* These two viruses are the most likely to cause severe disease in humans. EEE is the more severe; the mortality rate is 30% or more, and survivors experience a high incidence of brain damage, deafness, and other neurological problems. EEE is uncommon (its main mosquito vector prefers to feed

*A lengthy list of diseases—rabies and similar lyssavirus diseases, as well as the SARS, Ebola, Hendra, and Nipah viruses—are all now known, or strongly suspected, to be transmitted by bats. There are reasons why bats make good disease reservoirs: there are more than a thousand species to occupy various niches; they are long-lived (5 to 50 years), which lends them stability as a reservoir; they tend to roost in close assemblies, which facilitate viral spread; and they fly relatively long distances as they forage for food—some are even migratory. Finally, bats seem to be able to carry viruses for long periods without clearing the infection or becoming ill.

CLINICAL FOCUS

A Neurological Disease

As you read through this problem, you'll see questions that clinicians ask themselves as they proceed through a diagnosis and treatment. Try to answer each question before going on to the next one.

1. On September 30, Yolanda, a 10-year-old girl, has pain and stiffness in her right arm and temperature of 38.3°C (101°F). On October 3, she begins vomiting and has increased arm pain and numbness.
   What could these symptoms indicate?
2. The high fever could indicate some sort of bacterial or viral infection. Yolanda's pediatrician orders a rapid group A streptococcal antigen test, which is negative. Yolanda is hospitalized on October 7, when she has difficulty swallowing. Her tongue has a whitish coating and is protruding from her mouth.
   What infections are possible?
3. The whitish coating on her tongue could indicate mucosal candidiasis. Yolanda is given fluconazole to combat the fungus. On October 8, a lumbar puncture shows elevated numbers of white blood cells.
   What does this indicate?
4. An elevated white blood cell count in Yolanda's CSF indicates some type of microbial infection of the CNS. Yolanda is treated with vancomycin for meningoencephalitis. She then experiences hypersalivation and lethargy.
   What does this suggest? How would you confirm the disease?
5. Rabies is confirmed by direct fluorescent-antibody staining of a skin biopsy for rabies virus antigens. Yolanda dies on November 2. An abundance of rabies viral inclusions (Negri bodies) are seen in the brain stem (**Figure A**).
   How would you treat people who had contact with Yolanda in October and November?
6. Postexposure prophylaxis (PEP) is administered to 66 people, including 31 people in Yolanda's school.
   Did the delay in diagnosis affect the outcome of the disease?
7. Early diagnosis cannot usually save a patient; however, it may help minimize the number of potential exposures and the need for PEP.
   What else must be determined about this case?
8. In mid-June, Yolanda had awakened during the night and said a bat had flown into her bedroom window and bitten her. Her mother cleaned a small mark on the girl's arm with an over-the-counter antiseptic but assumed the incident was a nightmare. Two days later, an older sibling took a dead bat away from the yard. The mother did not associate the bat with the previous event and did not seek rabies PEP for the girl.

   The nucleotide sequence of the PCR product was used to identify a rabies virus variant associated with silver-haired bats (**Figure B**).
   Why is rabies surveillance and case reporting important in the United States?
9. During 2002–2013, 22 of 25 reported human rabies cases in the United States were epidemiologically linked to bats. Human rabies is preventable with proper wound care and timely, appropriate administration of human rabies immune globulin and rabies vaccine before onset of clinical symptoms.

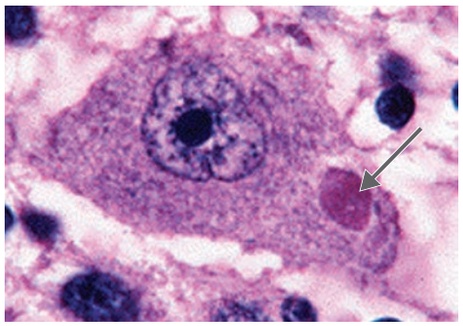


Figure A **Negri body at the arrow in an infected neuron.**



Figure B **Silver-haired bat.**

Source: Adapted from *MMWR* 62(32): 642–644, August 16, 2013.

on birds); only about 100 cases a year are reported. WEE has been only rarely reported in recent years and has a mortality rate estimated at about 5%.

St. Louis encephalitis (SLE) acquired its name from the location of an early major outbreak (in which it was originally discovered that mosquitoes are involved in the transmission of these diseases). SLE is distributed from southern Canada to Argentina, but mostly in the central and eastern United States. Fewer than 1% of people infected exhibit symptoms; it can, however, be a severe disease with a mortality rate in symptomatic patients of about 20%.

California encephalitis (CE) was first identified in that state, but most cases occur elsewhere. The La Crosse strain of CE (first isolated in La Crosse, Wisconsin) is the most commonly encountered arbovirus (**Figure 22.14**). A relatively mild illness, it is seldom fatal.

A new arbovirus disease, now well known, was introduced into the United States in 1999. First reported in the New York City area, it was quickly identified as being caused by *West Nile virus (WNV),* which, like the virus causing SLE, is related to the virus causing Japanese encephalitis (see page 626). The disease is maintained in a bird-mosquito-bird cycle. The primary mosquito is a species of *Culex,* which can overwinter as adults in temperate climates. Birds serve as amplifying hosts; some species, such as house sparrows, can have high levels of viremia

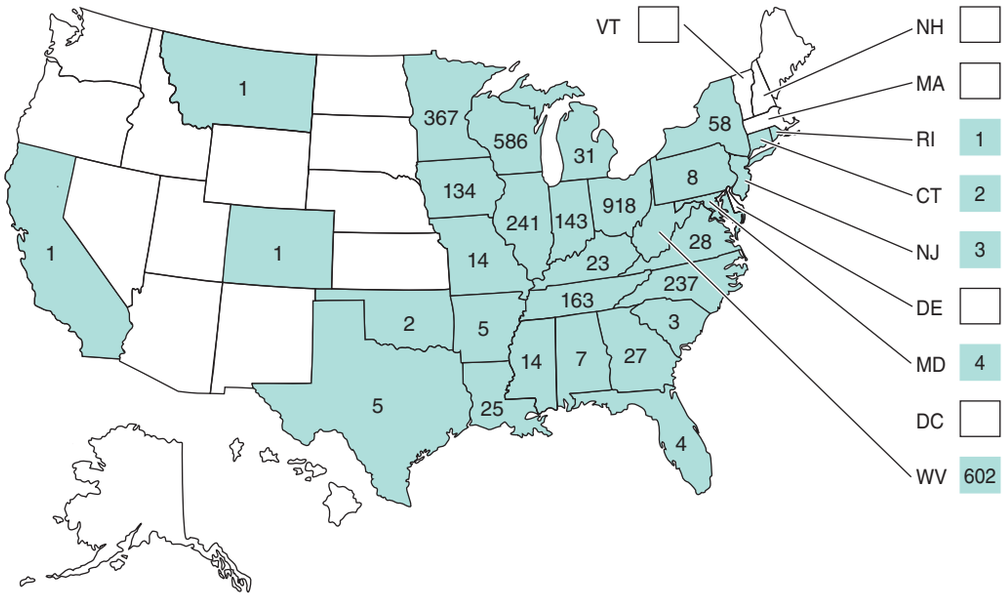


Figure 22.14 California serogroup arbovirus cases: 1964–2010. This is the most common arbovirus encephalititis in the United States. The majority of cases in this serogroup are of the La Crosse virus. *Source:* CDC 2014.

Q Why do arboviral infections occur during the summer months?

without dying. But mortality of infected crows, ravens, and blue jays is high, and public health officials sometimes request reports of dead birds of these species. Most human cases of WNV are subclinical or mild, but the disease can cause a polio-like paralysis or fatal encephalitis, especially in older adults. See Diseases in Focus 22.2 on page 628 for a summary of the arbovirus-caused diseases of the United States.

The Far East and South Asia also have endemic arboviral encephalitis. **Japanese encephalitis** is the best known; it is a serious public health problem, especially in Japan, Thailand, Korea, China, and India. Vaccines are used to control the disease in these countries and are often recommended for visitors. Only about 1% of people infected show clinical symptoms, which may involve seizures and paralysis—and a mortality rate of 20–30%.

Arboviral encephalitis is diagnosed by serological tests, usually ELISA tests to identify IgM antibodies. The most effective preventive measure is local control of the mosquitoes.

CHECK YOUR UNDERSTANDING

When there are serious local outbreaks of arboviral encephalitis, what is the usual response to minimize its transmission? **22-11**

Fungal Disease of the Nervous System

LEARNING OBJECTIVE

22-12 Identify the causative agent, reservoir, symptoms, and treatment for cryptococcosis.

The central nervous system is seldom invaded by fungi. However, one pathogenic fungus in the genus *Cryptococcus* is well adapted to growth in CNS fluids.

Cryptococcus neoformans Meningitis (Cryptococcosis)

The disease **cryptococcosis** is caused by fungi of the genus *Cryptococcus*. They form spherical cells resembling yeasts, reproduce by budding, and produce extremely heavy polysaccharide capsules (**Figure 22.15**). The primary species pathogenic for humans are *Cryptococcus neoformans* and *C. grubii*. These organisms are widely distributed, especially in areas contaminated by bird droppings most notably from pigeons, which excrete an estimated 25 pounds a year. The disease is transmitted mainly by the inhalation of dried, contaminated droppings. The inhaled fungi multiply in persons with compromised immune systems,

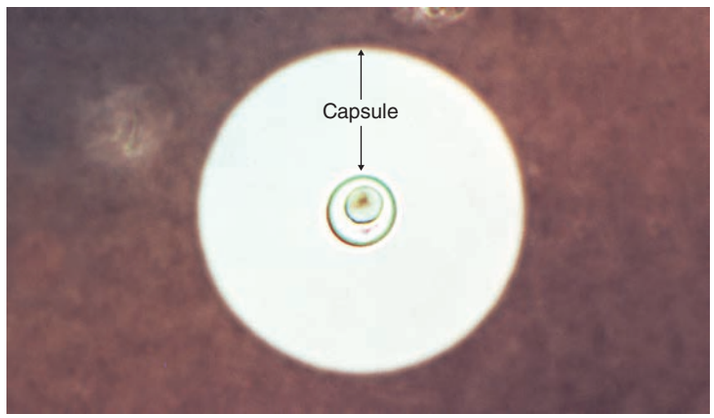


Figure 22.15 *Cryptococcus neoformans.* This yeastlike fungus has an unusually thick capsule. In this photomicrograph, the capsule is made visible by suspending the cells in dilute India ink.

Q What is the significance of the extremely heavy polysaccharide capsule found in *C. neoformans*?

such as AIDS patients, disseminate to the CNS, and cause meningitis that has a high mortality rate. In recent years there have been outbreaks of cryptococcosis in AIDS patients in California caused by *C. gattii* (GAHT-tē-ē), a species that had previously been reported only in tropical regions. However, an association has now been observed with trees native to subtropical and temperate regions, as well; the fungus inhabits an ecological niche in decayed hollows of mature trees. See the Clinical Case on page 321. From there the basidiospores (see page 327) can contaminate surrounding soils or be spread with the distribution of wood products. This species has now been isolated in cases of cryptococcosis, even in otherwise healthy individuals, in several areas of western North America as far north as Vancouver Island in Canada. This disease is likely to continue to spread southward and may eventually affect areas as far as Florida.

The best serological diagnostic test is a latex agglutination test to detect cryptococcal antigens in serum or cerebrospinal fluid. The drugs of choice for treatment are amphotericin B and flucytosine in combination. Even so, the mortality rate may approach 30%.

CHECK YOUR UNDERSTANDING

What is the most common source of airborne cryptococcal infections? **22-12**

Protozoan Diseases of the Nervous System

LEARNING OBJECTIVE

22-13 Identify the causative agent, vector, symptoms, and treatment for African trypanosomiasis and amebic meningoencephalitis.

Protozoa capable of invading the CNS are rare. However, those that can reach it cause devastating effects.

African Trypanosomiasis

African trypanosomiasis, or sleeping sickness, is a protozoan disease that affects the nervous system. In 1907, Winston Churchill described Uganda during an epidemic of sleeping sickness as a "beautiful garden of death." Even today, estimates are that as many as half a million Africans are infected, and there are about 100,000 new cases yearly.

The disease is caused by two subspecies of *Trypanosoma brucei* that infect humans: *Trypanosoma brucei gambiense* and *T.b. rhodesiense.* They are morphologically indistinguishable but differ significantly in their epidemiology—that is, in their ability to infect nonhuman hosts. Humans are the only significant reservoir for *T.b. gambiense,* whereas *T.b. rhodesiense* is a parasite of domestic livestock and many wild animals. These protozoans are flagellates (see Figure 23.22 on page 662 for the appearance of a similar organism) that are spread by tsetse fly vectors. *T.b. gambiense* is transmitted by a tsetse fly species that inhabits stream vegetation, where there are also concentrations of human populations. It is distributed throughout west and central Africa and is sometimes termed West African trypanosomiasis. More than 97% of reported cases in humans are of this type. Once a person becomes infected, there are few symptoms for weeks or months. Eventually, a chronic form of disease with fever, headaches, and a variety of other symptoms develops that indicates involvement and deterioration of the CNS. Coma and death are inevitable without effective treatment.

In contrast, infections by *T.b. rhodesiense* are transmitted by species of tsetse flies that inhabit savannahs (grasslands with scattered trees) of eastern and southern Africa. Wild animals inhabiting these areas are well adapted to the parasite and are little affected, but humans and domestic animals become acutely ill. This has had a profound effect on sub-Saharan Africa, an area nearly the size of the United States. Agricultural development has been practically prohibited because domestic food and working animals become infected. Infections of humans follow a more acute course than that caused by *T.b. gambiense;* symptoms of illness are apparent within a few days or so of infection. Death occurs within weeks or a few months, sometimes from cardiac problems even before the CNS is affected.

There are some moderately effective chemotherapeutic agents, such as suramin and pentamidine, but these do not alter the course of the disease once the CNS is affected. The drug that does alter the disease's course, melarsoprol, is very toxic. This toxicity has been vividly described: it "can melt plastic syringes, causes caustic burns, is extremely painful when injected, and kills about 5% of patients." In 1992 a new drug, eflornithine, was introduced that crosses the blood–brain barrier and blocks an enzyme required for proliferation of the parasite. It requires an extended series of injections, but it is so dramatically effective against even late stages of *T.b. gambiense* that it has been called the resurrection drug. (Its effectiveness against *T.b. rhodesiense* is variable; melarsoprol is still recommended.) The history of this drug provides a valuable illustration of problems in providing health services in poverty-stricken parts of the world. Because the only populations suffering from African trypanosomiasis were unable to afford it, production was soon discontinued. Happily, it was found that the drug had a profitable use in the industrial world: it reduces growth of unwanted facial hair on women. Because of this, the manufacturer has continued to supply eflornithine through the WHO at no cost.

The current primary approach in combating the disease is to attempt elimination of the vector, the tsetse fly. The use of tentlike, insecticide-treated traps that mimic the color and odor of animal hosts of the insect, combined with large-scale releases of sterile males have eliminated the tsetse fly on the offshore island of Zanzibar. (Female tsetse flies mate only once; the release of artificially reared, radiation-sterilized males in vast numbers prevents females that mate with them from producing young.) The insect is a weak flyer, and health

DISEASES IN FOCUS 22.2

Types of Arboviral Encephalitis

Arboviral encephalitis is usually characterized by fever, headache, and altered mental status ranging from confusion to coma. Vector control to decrease contacts between humans and mosquitoes is the best prevention. Mosquito control includes removing standing water and using insect repellent while outdoors. An 8-year-old girl in rural Wisconsin has chills, headache, and fever and reports having been bitten by mosquitoes. Use the table below to determine which types of encephalitis are most likely. How would you confirm your diagnosis? For the solution, go to MasteringMicrobiology.



Culex **mosquito engorged with human blood.**

Disease	Pathogen	Mosquito Vector	Reservoir	U.S. Distribution	Epidemiology	Mortality
Western Equine Encephalitis	WEE virus (*Togavirus*)	*Culex*	Birds, horses		Severe disease; frequent neurological damage, especially in infants	5%
Eastern Equine Encephalitis	EEE virus (*Togavirus*)	*Aedes, Culiseta*	Birds, horses		More severe than WEE; affects mostly young children and younger adults; relatively uncommon in humans	>30%
St. Louis Encephalitis	SLE virus (*Flavivirus*)	*Culex*	Birds		Mostly urban outbreaks; affects mainly adults over 40	20%
California Encephalitis	CE virus (*Bunyavirus*)	*Aedes*	Small mammals		Affects mostly 4- to 18-year age groups in rural or suburban areas; La Crosse strain medically most important. Rarely fatal; about 10% have neurological damage	1% of those hospitalized
West Nile Encephalitis	WN virus (*Flavivirus*)	Primarily *Culex*	Primarily birds, assorted rodents, and large mammals		Most cases asymptomatic—otherwise symptoms vary from mild to severe; likelihood of severe neurological symptoms, and fatality increases with age	4–18% of those hospitalized

care officials hope to repeat this eradication on selected areas of the mainland.

A vaccine is being developed, but a major obstacle is that the trypanosome is able to change protein coats at least 100 times and can thus evade antibodies aimed at only one or a few of the proteins. Each time the body's immune system is successful in suppressing the trypanosome, a new clone of parasites appears with a different antigenic coat (**Figure 22.16**).

Amebic Meningoencephalitis

There are two species of protozoa that cause amebic meningoencephalitis, a devastating disease of the nervous system. These

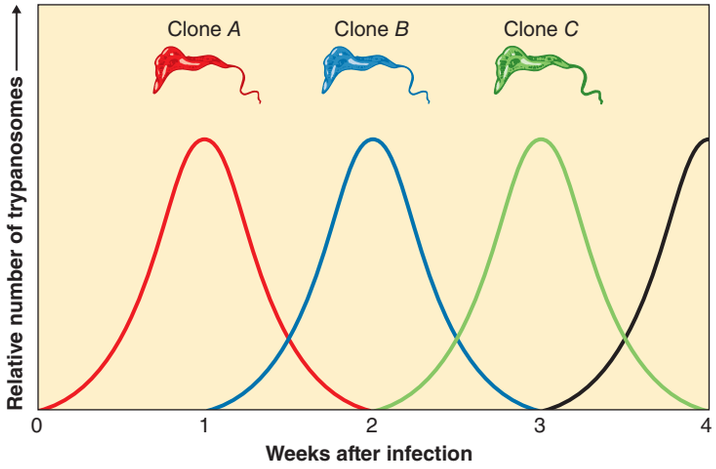
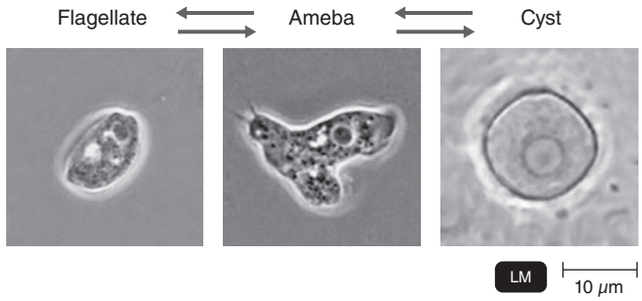


Figure 22.16 How trypanosomes evade the immune system. The population of each trypanosome clone drops nearly to zero as the immune system suppresses its members, but a new clone with a different antigenic surface then replaces the previous clone. The black line represents the population of clone *D*.

Q What viral disease that is causing a worldwide pandemic would make for a similar figure?

Clinical Case

The CSF fluid contains slow-moving ameboid cells. The technician performs an indirect immunofluoresence test to determine what specific microorganism is in Patricia's CSF. The test shows antibodies against *Naegleria fowleri* at a dilution of 1:4096. The news is serious: Patricia has primary amebic meningoencephalitis, usually a rapidly fatal disease. *N. fowleri* is a euglenozoa that lives as an ameba in warm freshwater. In low nutrients, the trophozoite forms a rapidly motile cell with two flagella. The trophozoite encysts during cold or dry conditions and reemerges when conditions improve (see the figure).



How is *N. fowleri* transmitted?

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protozoa are both found in recreational freshwater. Human exposure to them is apparently widespread; many in the population carry antibodies—fortunately, symptomatic disease is rare. *Naegleria fowleri* is a protozoan (ameba) that causes a neurological disease, **primary amebic meningoencephalitis (PAM)** (Figure 22.17). Although scattered cases are reported in most parts of the world, only a few cases are reported in the United States annually. The most common victims are children who swim in warm ponds or streams. The organism initially infects the nasal mucosa and later penetrates to the brain and proliferates, feeding on brain tissue. The fatality rate is nearly 100%, death occurring within a few days after symptoms appear. Because of the rarity of the disease, there is a low "index of suspicion"; also, the symptoms resemble those of encephalitis caused by other, more common, pathogens. Diagnosis is typically made at autopsy. There have been only a very few survivors of PAM. They were treated with a combination of several antibiotics.

A similar neurological disease is **granulomatous amebic encephalitis (GAE).** GAE is caused by a species of *Acanthamoeba,* but not the same one that causes *Acanthamoeba* keratitis, a serious disease affecting the eyes. It is chronic, slowly progressive, and fatal in a matter of weeks or months. GAE has an unknown incubation period, and months may elapse before symptoms appear. Granulomas (see Figure 23.28, page 670) form around

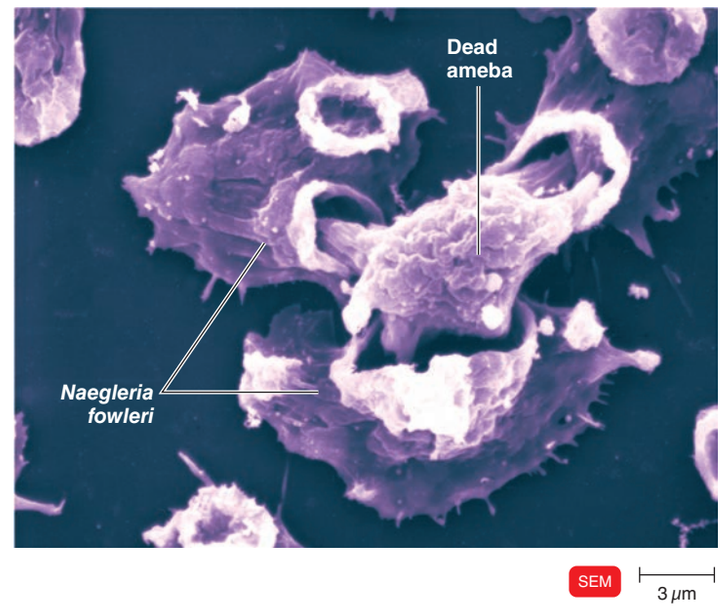


Figure 22.17 *Naegleria fowleri*. This photo shows two vegetative stages of *N. fowleri* beginning to devour a presumably dead ameba. The suckerlike structures (called amebastomes) function in phagocytic feeding—usually on bacteria or assorted debris that may include host tissue. This protozoan also has a spherical cyst stage and an ovoid flagellated stage (which is most likely to be the infective form) that allows it to swim rapidly in its aquatic habitat.

Q How is amebic meningoencephalitis transmitted?

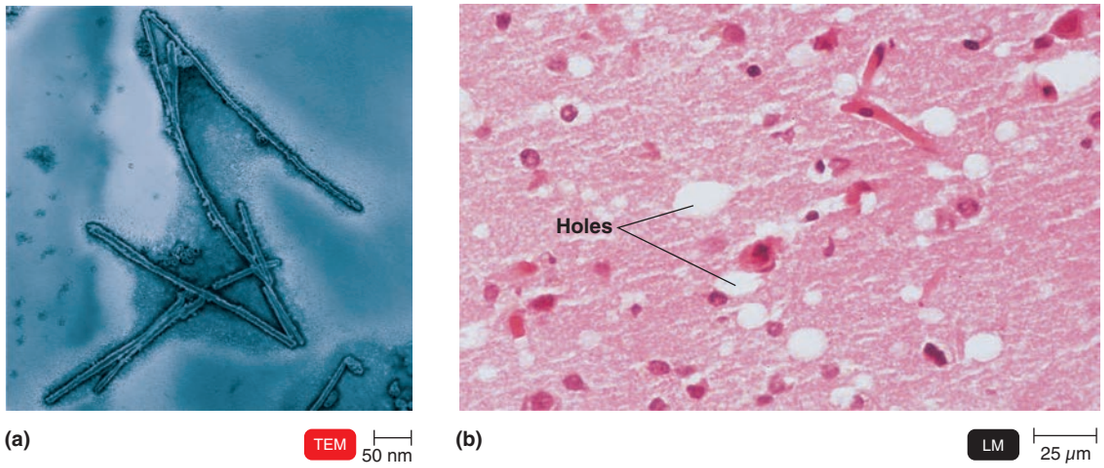


Figure 22.18 Spongiform encephalopathies. These diseases, caused by prions, include bovine spongiform encephalopathy, scrapie in sheep, and Creutzfeldt-Jakob disease in humans. All are similar in their pathology. **(a)** Brain tissue showing characteristic fibrils produced by prion diseases. These fibrils are insoluble aggregates of abnormally folded proteins (prions). Individual prions are not visible by any known technology. **(b)** Brain tissue showing the clear holes that give it a spongiform appearance.

Q What are prions?

the organism in response to an immune reaction. The portal of entry is not known but is probably mucous membranes. Multiple lesions are formed in the brain and other organs, especially the lungs. It is probable that many cases of GAE ascribed to *Acanthamoeba* were actually caused by another, similar protozoan, *Balamuthia mandrillaris,* which was first reported in a mandrill baboon in 1989.

CHECK YOUR UNDERSTANDING

What insect is the vector for African trypanosomiasis? **22-13**

Nervous System Diseases Caused by Prions

LEARNING OBJECTIVE

22-14 List the characteristics of diseases caused by prions.

Several fatal diseases affecting the human central nervous system are caused by prions. To explain the term *prion,* we need to recall from the discussion of enzymes in Chapter 5 that the shape of the enzyme's protein component is essential for its operation. A certain protein is normally found on the surface of brain cell neurons and is even found on the surface of certain stem cells in red bone marrow and cells that become neurons; let's call it *normal protein.* Its function is uncertain, but there is evidence that it may guide maturation of nerve cells. Certainly, the protein's shape causes no damage. But this protein can assume two folded shapes, one normal and the other abnormal (there is no change in the amino acid sequence). If the *normal protein* encounters an *abnormally folded protein,* a **prion,** the normal protein changes its shape and also becomes abnormally folded—that is, another prion. In fact, a chain reaction of protein misfolding occurs. Therefore, a single infective prion may lead to a cascade of new prions, which then clump together to form the fibril aggregations of misfolded proteins that are found in diseased brains. See **Figure 22.18a**. Autopsies of this infected brain tissue also show that it exhibits a characteristic spongiform degeneration (it is porous, like a sponge), as shown in Figure 22.18b. (Also see the discussion of prions in Chapter 13, page 383, and Figure 13.22.) In recent years the study of these diseases, called **transmissible spongiform encephalopathies (TSE),** has been one of the most interesting areas of medical microbiology.

A typical prion disease in animals is **sheep scrapie,** which has been long known in Great Britain and made its first appearance in the United States in 1947. The infected animal scrapes itself against fences and walls until areas of its body are raw. During a period of several weeks or months, the animal gradually loses motor control and dies. The infection can be experimentally passed to other animals by injection of brain tissue from one animal to the next. Similar conditions are seen in mink, possibly resulting from the animals' being fed mutton. A prion disease, **chronic wasting disease,** affects wild deer and elk in the western United States and Canada. It is invariably fatal, and there are concerns that it might infect humans who eat venison and might eventually infect domestic livestock.

Humans suffer from TSE diseases similar to scrapie; **Creutzfeldt-Jakob disease (CJD)** is an example. CJD is rare (about 200 cases per year in the United States). It often occurs in families, an indication of a genetic component. This form of CJD is sometimes referred to as classic CJD to differentiate it from similar variants that have appeared. There is no doubt that an infective agent is involved because transmission via corneal transplants and accidental scalpel nicks of a surgeon during

TABLE 22.1 Comparative Characteristics of Classic and Variant Creutzfeldt-Jakob Disease

Characteristic	Classic CJD	Variant CJD
Median Age at Death (yr)	68 (range 23–97)	28 (range 14–74)
Median Duration of Illness (mo)	4 to 5	13 to 14
Clinical Presentation	Dementia; early neurological signs	Prominent psychiatric and behavioral symptoms; delayed neurological signs
Genotype*	Other amino acid combinations	Methionine/methionine

*Victims are homozygous at codon 129, that is, both of their PrP genes (one from each parent) have methionine coded at this position. This is characteristic of only about 37% of Caucasians. Other members of this population have different amino acid combinations at this position—and, although a handful of cases that have appeared were exceptions (homozygous valine/valine, or heterozygous methionine/valine), no one with these genotypes has contracted vCJD to date.

autopsy have been reported. Several cases have been traced to the injection of a growth hormone derived from human tissue. Boiling and irradiation have no effect, and even routine autoclaving is not reliable. This has led to suggestions that surgeons use disposable instruments where there is a risk of exposure to CJD. To sterilize reusable instruments, the WHO currently recommends a strong solution of sodium hydroxide combined with extended autoclaving at 134°C. However, there are reports that applications of a simple cleaning detergent combined with protease enzymes to disrupt the prions may prove an effective solution to the problem.

Some tribes in New Guinea have suffered from a TSE disease called **kuru** (a native word for shaking or trembling). Transmission of kuru is apparently related to the practice of cannibalistic rituals. Carleton Gajdusek received the Nobel Prize for Physiology and Medicine in 1976 for his investigations of kuru. The disease is disappearing as the practice of ritualistic cannibalism dies out.

Bovine Spongiform Encephalopathy and Variant Creutzfeldt-Jakob Disease

A TSE that is much in the news is **bovine spongiform encephalopathy (BSE).** The disease is better known as *mad cow disease* because of the behavior of the animals. The outbreak that began in 1986 in Great Britain was eventually controlled by drastic culling of herds. The origin of the disease is usually ascribed to feed supplements containing meat and bone meal contaminated with prions from sheep infected with scrapie, a long-endemic neurological disease. Another hypothesis proposes that BSE resulted from a spontaneous mutation in a cow and that there is no connection with scrapie.

There is an urgent need for reliable tests that will diagnose cases of BSE in early, nonsymptomatic stages in live animals. Currently, the only available tests require postmortem brain tissue and detect only late stages of the disease. In attempts to prevent introduction of BSE into the United States, there are rules prohibiting the use of meat from "downer" animals (fallen and unable to rise and walk) for any purpose and the use of animal protein as a feed supplement. The FDA has banned for human consumption certain portions of the cattle carcass that are most likely to contain a neurological pathogen. Only a small percentage of animal carcasses in the United States are tested for BSE—in Europe and Japan, practically all slaughtered animals are tested.

If this disease were to establish itself in domestic cattle in the United States, it would be economically devastating. However, there is another aspect—that the disease could be passed on to humans. In Great Britain and a few other locales around the world, a few cases of apparent classic CJD appeared in relatively young humans. CJD rarely occurs in this age group, and a connection with BSE was feared. Investigation also showed that this variant of CJD (vCJD) differed in significant ways from classic CJD (Table 22.1). A few hundred cases have been identified so far. Considering the long incubation times of prion diseases and that an estimated 1 million cattle had been infected with BSE, it was feared that large numbers of vCJD cases might eventually

Clinical Case

Cysts can be inhaled with dust, and amebae can be forced into the nose when a swimmer dives underwater. The ameba crosses the nasal mucosa to enter the central nervous system. The ameba secretes hydrolytic enzymes that digest the nasal mucosa and nerve cells, allowing it to enter the subarachnoid space. The ameba then feeds on the digested nerve cells. A week earlier, Patricia and her family had been swimming in Deep Creek Hot Springs. The little girl did not heed the sign warning swimmers to keep their head above water. The attending physician also tests Patricia's parents for their antibody titers. Patricia's father has a low (1:16) antibody titer against *N. fowleri* but is not ill; her mother's serum is negative for antibody.

What is the treatment for amebic meningoencephalitis?

DISEASES IN FOCUS 22.3

Microbial Diseases with Neurological Symptoms or Paralysis

After eating canned chili, two children experience cranial nerve paralysis followed by descending paralysis. The children are on mechanical ventilation. Leftover canned chili is tested by mouse bioassay. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Gram stain from canned chili.

Disease	Pathogen	Symptoms	Method of Transmission	Treatment	Prevention
BACTERIAL DISEASES					
Tetanus	*Clostridium tetani*	Lockjaw; muscle spasms	Puncture wound	Tetanus immune globulin; antibiotics	Toxoid vaccine (DTaP, Td)
Botulism	*Clostridium botulinum*	Flaccid paralysis	Foodborne intoxication	Antitoxin	Proper canning of foods; infants should not eat honey
Leprosy	*Mycobacterium leprae, M. lepromatosis*	Loss of sensation in skin; disfiguring nodules	Prolonged contact with contaminated secretions	Dapsone, rifampin, clofaximine	Possibly BCG vaccine
VIRAL DISEASES					
Poliomyelitis	Poliovirus	Headache, sore throat, stiff neck; paralysis if motor nerves infected	Ingesting contaminated water (fecal–oral route)	Mechanical breathing aid	Inactivated polio vaccine (IPV)
Rabies	*Lyssavirus*	Fatal infection; agitation, muscle spasms, difficulty swallowing	Animal bite	Postexposure treatment: rabies immunoglobulin plus vaccine	Human diploid cell vaccine for high-risk individuals; vaccination of domestic animals
PROTOZOAN DISEASE					
African Trypanosomiasis	*Trypanosoma brucei rhodesiense, T. b. gambiense*	Fatal infection; early symptoms (headache, fever) progress to coma	Tsetse fly	Suramin; pentamidine	Vector control
PRION DISEASES					
Creutzfeldt-Jakob Disease	Prion	Fatal infection; neurologic symptoms include trembling	Inherited; ingested; transplants	None	None
Kuru	Prion	Same as Creutzfeldt-Jakob disease	Contact or ingestion	None	None

appear. However, this concern has subsided, especially since the number of cases declined from a small peak in 2000 and after it was shown that the affected patients shared a certain limited genetic profile.

CHECK YOUR UNDERSTANDING

- What are the recommendations for sterilizing reusable surgical instruments when prion contamination might be a factor? **22-14**

Disease Caused by Unidentified Agents

LEARNING OBJECTIVE

22-15 List some possible causes of chronic fatigue syndrome.

Chronic Fatigue Syndrome

The medical community has long been puzzled by patients who complain of persistent fatigue that prevents them from working and has no apparent cause. They often complain as well of multiple allergies. Called **chronic fatigue syndrome (CFS),** the debilitating condition continues for months or years. For many years, the condition was dismissed as a complaint of people who were depressed or simply complaining about trivial symptoms. Recent research on CFS, however, suggests that it is not "all in the mind" but rather is strongly linked to the immune system and may also have a genetic component. There is now an alternative, more impressive name, *myalgic encephalomyelitis (ME).* People complaining of CFS often do not adapt well to daily stresses and do not respond strongly to fight infections. CFS often begins with a flulike illness that seems never to go away. Some think that it is triggered by viral illnesses, such as infectious mononucleosis (caused by the Epstein-Barr virus), Q fever, Lyme disease, and others. In 2010, there were reports that CFS patients are often infected with a retrovirus termed XMRV. This is a member of a group of viruses called *murine leukemia virus–related viruses (MLV),* which are known to cause neurological problems in mice. However, other laboratories were unable to confirm this. The most recent speculation was prompted when fragments of *Bartonella henselae* bacteria, the pathogen causing cat-scratch disease, were found in many CFS patients. The elusiveness of this pathogen, which hides inside blood vessels and changes its immunological character rapidly, has made it an attractive candidate.

The CDC has now developed a diagnostic definition for CFS: a persistent, unexplained fatigue that lasts at least 6 months. The patient should also exhibit at least four of a list of symptoms including sore throat, tender lymph nodes, muscle pain, pain in multiple joints, headaches, unrefreshing sleep, malaise after exercise, and impaired short-term memory or concentration. The condition is not uncommon in the United States; the prevalence is 0.52% in women and 0.29% in men, totaling an estimated 800,000 to 2.5 million persons.

There is no approved treatment for CFS, but an experimental drug, Ampligen, is being tested. It is designed to stimulate production of antiviral interferons.

CHECK YOUR UNDERSTANDING

Name one common disease that may be associated with chronic fatigue syndrome. **22-15**

* * *

Diseases in Focus 22.3 summarizes the main causes of microbial disease involving neurological symptoms and paralysis.

Clinical Case Resolved

Patricia is treated with the antibiotics amphothericin B and rifampin. *N. fowleri* are widespread, but infection is rare. As many as 100 amebae per liter of water may be necessary for infection. Inapparent infection is not uncommon, and the father's low antibody titer suggests he does have an infection. Patricia is one of fewer than 10 patients reported to survive primary amebic meningoencephalitis. Patricia survives because of the laboratory technician's quick thinking; her infection is diagnosed early, and she is placed on antiamebic therapy immediately.

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Structure and Function of the Nervous System (pp. 608–609)

1. The central nervous system (CNS) consists of the brain, which is protected by the skull bones, and the spinal cord, which is protected by the backbone.
2. The peripheral nervous system (PNS) consists of the nerves that branch from the CNS.
3. The CNS is covered by three layers of membranes called meninges: the dura mater, arachnoid mater, and pia mater. Cerebrospinal fluid (CSF) circulates between the arachnoid mater and the pia mater in the subarachnoid space.
4. The blood–brain barrier normally prevents many substances, including antibiotics, from entering the brain.
5. Microorganisms can enter the CNS through trauma, along peripheral nerves, and through the bloodstream and lymphatic system.
6. An infection of the meninges is called meningitis. An infection of the brain is called encephalitis.

Bacterial Diseases of the Nervous System (pp. 609–618)

Bacterial Meningitis (pp. 609–613)

1. Meningitis can be caused by viruses, bacteria, fungi, and protozoa.

2. The three major causes of bacterial meningitis are *Haemophilus influenzae, Streptococcus pneumoniae,* and *Neisseria meningitidis.*
3. Nearly 50 other species of opportunistic bacteria can cause meningitis.
4. *H. influenzae* is part of the normal throat microbiota. It requires blood factors for growth; serotypes are based on capsules.
5. *H. influenzae* type b is the most common cause of meningitis in children under 4 years old.
6. An Hib conjugated vaccine directed against the capsular polysaccharide antigen is available.
7. *N. meningitidis* causes meningococcal meningitis. This bacterium is found in the throats of healthy carriers and is transmitted by droplet aerosols or direct contact with secretions.
8. Meningococci probably gain access to the meninges through the bloodstream. The bacteria may be found in leukocytes in CSF.
9. A purified capsular polysaccharide vaccine against serotypes A, C, Y, and W-135 is available.
10. *S. pneumoniae* is commonly found in the nasopharynx.
11. Young children are most susceptible to *S. pneumoniae* meningitis. Untreated, it has a high mortality rate.
12. A *S. pneumoniae* conjugated vaccine is available.
13. *Listeria monocytogenes* causes meningitis in newborns, the immunosuppressed, pregnant women, and cancer patients.
14. Acquired by ingestion of contaminated food, listeriosis may be asymptomatic in healthy adults.
15. *L. monocytogenes* can cross the placenta and cause spontaneous abortion and stillbirth.

Tetanus (pp. 613–614)

16. Tetanus is caused by an exotoxin produced by *Clostridium tetani.*
17. *C. tetani* produces the neurotoxin tetanospasmin, which causes the symptoms of tetanus: spasms, contraction of muscles controlling the jaw, and death resulting from spasms of respiratory muscles.
18. Acquired immunity results from DTaP immunization.
19. Following an injury, an immunized person may receive a booster of tetanus toxoid. An unimmunized person may receive (human) tetanus immune globulin.
20. Debridement (removal of tissue) and antibiotics may be used to control the infection.

Botulism (pp. 614–617)

21. Botulism is caused by an exotoxin produced by *C. botulinum* growing in foods.
22. Serological types of botulinum toxin vary in virulence; type A is the most virulent.
23. The toxin is a neurotoxin that inhibits the transmission of nerve impulses.
24. Blurred vision occurs in 1 to 2 days; progressive flaccid paralysis follows for 1 to 10 days, possibly resulting in death from respiratory and cardiac failure.
25. *C. botulinum* will not grow in acidic foods or in an aerobic environment. Endospores are killed by proper canning. Adding nitrites to foods inhibits growth of *C. botulinum*.
26. The toxin is heat labile and is destroyed by boiling (100°C) for 5 minutes.
27. Infant botulism results from the growth of *C. botulinum* in an infant's intestines.
28. Wound botulism occurs when *C. botulinum* grows in anaerobic wounds.
29. For diagnosis, mice protected with antitoxin are inoculated with toxin from the patient or foods.

Leprosy (pp. 617–618)

30. Leprosy, or Hansen's disease, is caused by *Mycobacterium leprae* or *M. lepromatosis*.
31. These bacteria have never been cultured on artificial media. They can be cultured in armadillos and mouse footpads.
32. The tuberculoid form of the disease is characterized by loss of sensation in the skin surrounded by nodules.
33. In the lepromatous form, disseminated nodules and tissue necrosis occur.
34. Leprosy is not highly contagious and is spread by prolonged contact with exudates.
35. Untreated individuals often die of secondary bacterial complications, such as tuberculosis.
36. Laboratory diagnosis is based on observations of acid-fast rods in a skin biopsy.

Viral Diseases of the Nervous System (pp. 618–626)

Poliomyelitis (pp. 618–620)

1. The symptoms of poliomyelitis are usually sore throat and nausea, and occasionally paralysis (fewer than 1% of cases).
2. Poliovirus is transmitted by the ingestion of water contaminated with feces.
3. Poliovirus first invades lymph nodes of the neck and small intestine. Viremia and spinal cord involvement may follow.
4. Diagnosis is based on isolation of the virus from feces and throat secretions.
5. The Salk vaccine (an inactivated polio vaccine [IPV]) involves the injection of formalin-inactivated viruses and boosters every few years. The Sabin vaccine (an oral polio vaccine [OPV]) contains three live, attenuated strains of poliovirus and is administered orally.
6. Polio is a good candidate for elimination through vaccination.

Rabies (pp. 620–624)

7. Rabies virus (*Lyssavirus*) causes an acute, usually fatal, encephalitis called rabies.
8. Rabies may be contracted through the bite of a rabid animal or invasion through skin. The virus multiplies in skeletal muscle and connective tissue.
9. Encephalitis occurs when the virus moves along peripheral nerves to the CNS.
10. Symptoms of rabies include spasms of mouth and throat muscles followed by extensive brain and spinal cord damage and death.
11. Laboratory diagnosis may be made by DFA tests of saliva, serum, and CSF or brain smears.
12. Reservoirs for rabies in the United States include skunks, bats, foxes, and raccoons. Domestic cattle, dogs, and cats may get rabies. Rodents and rabbits seldom get rabies.
13. Postexposure treatment includes administration of human rabies immune globulin (RIG) along with multiple intramuscular injections of vaccine.

14. Preexposure treatment consists of vaccination.
15. Other genotypes of *Lyssavirus* cause rabies-like diseases.

Arboviral Encephalitis (pp. 624–626)

16. Symptoms of encephalitis are chills, headache, fever, and eventually coma.
17. Many types of viruses transmitted by mosquitoes (called arboviruses) cause encephalitis.
18. The incidence of arboviral encephalitis increases in the summer months, when mosquitoes are most numerous.
19. Notifiable arboviral infections are eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis (SLE), California encephalitis (CE), and West Nile virus (WNV).
20. Diagnosis is based on serological tests.
21. Control of the mosquito vector is the most effective way to control encephalitis.

Fungal Disease of the Nervous System (pp. 626–627)

***Cryptococcus neoformans* Meningitis (Cryptococcosis)** (pp. 626–627)

1. *Cryptococcus* spp. are encapsulated yeastlike fungi that cause cryptococcosis.
2. The disease may be contracted by inhaling dried infected pigeon or chicken droppings.
3. The disease begins as a lung infection and may spread to the brain and meninges.
4. Immunosuppressed individuals are most susceptible to cryptococcosis.
5. Diagnosis is based on latex agglutination tests for cryptococcal antigens in serum or CSF.

Protozoan Diseases of the Nervous System (pp. 627–630)

African Trypanosomiasis (pp. 627–628)

1. African trypanosomiasis is caused by the protozoa *Trypanosoma brucei gambiense* and *T.b. rhodesiense* and is transmitted by the bite of the tsetse fly.
2. The disease affects the nervous system of the human host, causing lethargy and eventually coma. It is commonly called sleeping sickness.
3. Vaccine development is hindered by the protozoan's ability to change its surface antigens.

Amebic Meningoencephalitis (pp. 628–630)

4. Encephalitis caused by the protozoan *Naegleria fowleri* is almost always fatal.
5. Granulomatous amebic encephalitis, caused by *Acanthamoeba* spp. and *Balamuthia mandrillaris,* is a chronic disease.

Nervous System Diseases Caused by Prions (pp. 630–632)

1. Prions are self-replicating proteins with no detectable nucleic acid.
2. Diseases of the CNS that progress slowly and cause spongiform degeneration are caused by prions.
3. Transmissible spongiform encephalopathies are caused by prions that are transferable from one animal to another.
4. Creutzfeldt-Jakob disease and kuru are human diseases similar to scrapie. They are transmitted between humans.

Disease Caused by Unidentified Agents (pp. 632–633)

Chronic Fatigue Syndrome (p. 633)

1. Chronic fatigue syndrome may be triggered by a microbial infection.

Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. If *Clostridium tetani* is relatively sensitive to penicillin, why doesn't penicillin cure tetanus?
2. What treatment is used against tetanus under the following conditions?
   a. before a person suffers a deep puncture wound
   b. after a person suffers a deep puncture wound
3. Why is the following description used for wounds that are susceptible to *C. tetani* infection: "… Improperly cleaned deep puncture wounds… ones with little or no bleeding . . ."?
4. Provide the following information on poliomyelitis: etiology, method of transmission, symptoms, prevention. Why aren't the Salk and Sabin vaccines considered treatments for poliomyelitis?
5. Fill in the following table:

Causative Agent of Meningitis	Susceptible Population	Transmission	Treatment
N. meningitidis			
H. influenzae			
S. pneumoniae			
L. monocytogenes			
C. neoformans			

6. Fill in the following table.

Disease	Etiology	Transmission	Symptoms	Treatment
Arboviral encephalitis				
African trypanosomiasis				
Botulism				
Leprosy				

7. DRAW IT On the figure below, identify the portal of entry of *H. influenzae, C. tetani,* botulinum toxin, *M. leprae,* poliovirus, *Lyssavirus,* arboviruses, and *Acanthamoeba.*



8. Outline the procedures for treating rabies after exposure. Outline the procedures for preventing rabies prior to exposure. What is the reason for the differences in the procedures?
9. Provide evidence that Creutzfeldt-Jakob disease is caused by a transmissible agent.
10. NAME IT This organism causes meningitis and is transmitted mainly by the inhalation of dried, contaminated bird droppings. Infections are treated with amphotericin B and flucytosine.

Multiple Choice

1. Which of the following is *false*?
   a. Only puncture wounds by rusty nails result in tetanus.
   b. Rabies is seldom found in rodents (e.g., rats, mice).
   c. Polio is transmitted by the fecal–oral route.
   d. Arboviral encephalitis is rather common in the United States.
   e. All of the above are true.
2. Which of the following does *not* have an animal reservoir or vector?
   a. listeriosis
   b. cryptococcosis
   c. amebic meningoencephalitis
   d. rabies
   e. African trypanosomiasis
3. A 12-year-old girl hospitalized for Guillain-Barré syndrome had a 4-day history of headache, dizziness, fever, sore throat, and weakness of legs. Seizures began 2 weeks later. Bacterial cultures were negative. She died 3 weeks after hospitalization. An autopsy revealed inclusions in brain cells that tested positive in an immunofluoresence test. She probably had
   a. rabies.
   b. Creutzfeldt-Jakob disease.
   c. botulism.
   d. tetanus.
   e. leprosy.
4. After receiving a corneal transplant, a woman developed dementia and loss of motor function; she then became comatose and died. Cultures were negative. Serological tests were negative. Autopsy revealed spongiform degeneration of her brain. She most likely had
   a. rabies.
   b. Creutzfeldt-Jakob disease.
   c. botulism.
   d. tetanus.
   e. leprosy.
5. Endotoxin is responsible for symptoms caused by which of the following organisms?
   a. *N. meningitidis*
   b. *S. pyogenes*
   c. *L. monocytogenes*
   d. *C. tetani*
   e. *C. botulinum*
6. The increased incidence of encephalitis in the summer months is due to
   a. maturation of the viruses.
   b. increased temperature.
   c. the presence of adult mosquitoes.
   d. an increased population of birds.
   e. an increased population of horses.

Match the following choices to the statements in questions 7 and 8:

a. antirabies antibodies
b. HDVC

7. Produces longest lasting protection.
8. Used for passive immunization.

Use the following choices to answer questions 9 and 10:

a. *Cryptococcus*
b. *Haemophilus*
c. *Listeria*
d. *Naegleria*
e. *Neisseria*

9. Microscopic examination of cerebrospinal fluid reveals gram-positive rods.
10. Microscopic examination of cerebrospinal fluid from a person who washes windows on a building in a large city reveals ovoid cells.

Analysis

1. Most of us have been told that a rusty nail causes tetanus. What do you suppose is the origin of this adage?
2. OPV is no longer used for routine vaccination. Provide the rationale for this policy.

Clinical Applications and Evaluation

1. A 1-year-old infant was lethargic and had a fever. When admitted to the hospital, he had multiple brain abscesses with gram-negative coccobacilli. Identify the disease, etiology, and treatment.
2. A 40-year-old bird handler was admitted to the hospital with soreness over his upper jaw, progressive vision loss, and bladder dysfunction. He had been well 2 months earlier. Within weeks he lost reflexes in his lower extremities and subsequently died. Examination of CSF showed lymphocytes. What etiology do you suspect? What further information do you need?
3. A normal baby gained weight appropriately for 12 weeks. Then she stopped feeding. Her right eardrum was inflamed, she had a stiff neck, and her temperature was 40°C. Examination of CSF revealed Gram-negative coccobacilli. Identify the disease and treatment.



In the Clinic

As an obstetrics nurse, you find out that one of your patients developed mononucleosis-like symptoms during pregnancy. **What testing is now necessary? Why? What advice should pregnant women receive to prevent this infection?**

Hint: Read about congenital infections on pages 657 and 663.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

23

Microbial Diseases of the Cardiovascular and Lymphatic Systems

The cardiovascular system consists of the heart, blood, and blood vessels. The lymphatic system consists of the lymph, lymph vessels, lymph nodes, and the lymphoid organs, which include the tonsils, appendix, spleen, and thymus. Fluids in both systems circulate throughout the body, intimately contacting many tissues and organs. The blood and lymph distribute nutrients and oxygen to body tissues, carrying away wastes. However, these same qualities make the cardiovascular and lymphatic systems vehicles for the spread of pathogens that enter their circulation when an insect bite, needle, or wound penetrates the skin. Because of this, many of the body's defensive systems are found in the blood and lymph. Circulating phagocytic cells are especially important; these are also in fixed locations such as the lymph nodes and spleen. The blood is an important part of our adaptive immune system; antibodies and specialized cells circulate to intercept pathogens introduced into the blood. Occasionally the defensive systems found in the blood are overwhelmed, however, and pathogens proliferate explosively with disastrous results. Dengue virus (shown in the photograph) is one such pathogen, and it grows in the immune system's macrophages. Dengue is described in the Clinical Case in this chapter.

Dengue virus (blue) in cells.

Structure and Function of the Cardiovascular and Lymphatic Systems

LEARNING OBJECTIVE

23-1 Identify the role of the cardiovascular and lymphatic systems in spreading and eliminating infections.

The center of the **cardiovascular system** is the heart (Figure 23.1). The function of the cardiovascular system is to circulate blood through the body's tissues so it can deliver certain substances to cells and remove other substances from them.

Blood is a mixture of formed elements (see Table 16.1, page 447) and a liquid called blood plasma. The **lymphatic system** is an essential part of the circulation of blood (Figure 23.2). As the blood circulates, some blood plasma filters out of the blood capillaries into spaces between tissue cells called *interstitial spaces.* The circulating fluid in the interstitial spaces is called *interstitial fluid.* Microscopic lymphatic vessels that surround tissue cells are called *lymph capillaries.* As the interstitial fluid moves around the tissue cells, it's picked up by the lymph capillaries; the fluid is then called *lymph.*

Because lymph capillaries are very permeable, they readily pick up microorganisms or their products. From lymph capillaries, lymph is transported into larger lymph vessels called *lymphatics,* which contain valves that keep the lymph moving toward the heart. Eventually, all the lymph is returned to the blood just before the blood enters the heart. As a result of this circulation, proteins and fluid that have filtered from the plasma are returned to the blood.

At various points in the lymphatic system are oval structures called *lymph nodes* (bean-shaped bodies ranging in size from a few millimeters to as much as 2 cm), through which lymph flows. (Also, see Figure 16.5, page 448.) Within the lymph nodes are fixed macrophages that help clear the lymph of infectious microorganisms. At times the lymph nodes themselves get infected and become visibly swollen and tender; swollen lymph nodes are called **buboes** (see Figure 23.10, page 649).

Lymph nodes are also an important component of the body's immune system. Foreign microbes entering lymph nodes encounter two types of lymphocytes: B cells, which

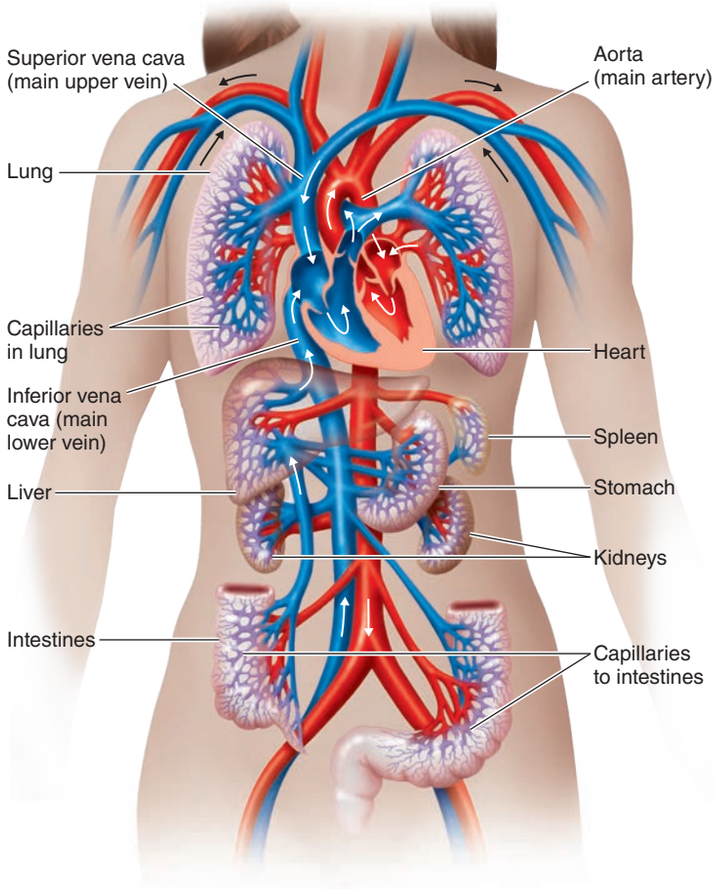


Figure 23.1 The human cardiovascular system and related structures. Details of circulation to the head and extremities are not shown in this simplified diagram. The blood circulates from the heart through the arterial system (red) to the capillaries (purple) in the lungs and other parts of the body. From these capillaries, the blood returns through the venous system (blue) to the heart.

Q How can a focal infection become systemic?

Clinical Case: Mosquito Mishap

Katie Tanaka, a normally healthy 34-year-old, has just returned to Rochester, New York, from a 1-week trip to Key West, Florida. Although Katie knows she should be a little tired after the long trip, she is surprised to feel so run down one day after she gets home. Katie makes an appointment with her primary care physician that afternoon, when she develops a fever, headache, and chills. Her doctor orders a urinalysis; the results reveal the presence of bacteria and red blood cells in her urine. Katie's doctor diagnoses her with a urinary tract infection and prescribes antibiotics.

Two days later, Katie returns to her primary care physician with a worsening headache, pain in the back of the eye made worse by eye movement, and complaints of feeling lightheaded, although her fever has resolved. Katie is alert and oriented but has substantial discomfort from her headache. When she is asked to close her eyes and stand with her feet together (touching each other), Katie begins swaying, which is a possible indicator of a brain lesion.

What infections are possible? Read on to find out.

638 655 660 664 670

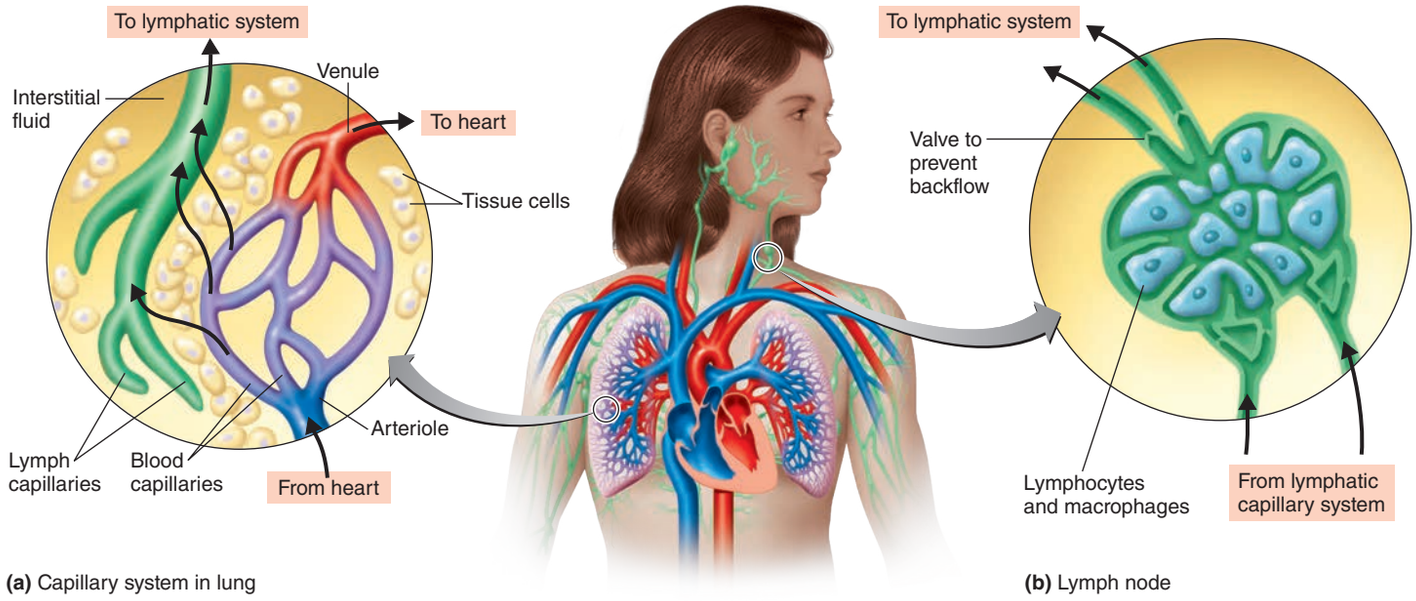


Figure 23.2 The relationship between the cardiovascular and lymphatic systems.
(a) From the blood capillaries, some blood plasma filters into the surrounding tissue where it is called interstitial fluid and enters the lymph capillaries. This fluid, now called lymph, returns to the heart through the lymphatic circulatory system (green), which channels the lymph to a vein. **(b)** All lymph returning to the heart must pass through at least one lymph node. (See also Figure 16.5, page 448.)

Q What is the role of the lymphatic system in defense against infection?

are stimulated to become plasma cells that produce humoral antibodies; and T cells, which then differentiate into effector T cells that are essential to the cell-mediated immune system.

CHECK YOUR UNDERSTANDING

Why is the lymphatic system so valuable for the working of the immune system? **23-1**

Bacterial Diseases of the Cardiovascular and Lymphatic Systems

LEARNING OBJECTIVES

23-2 List the signs and symptoms of sepsis, and explain the importance of infections that develop into septic shock.
23-3 Differentiate gram-negative sepsis, gram-positive sepsis, and puerperal sepsis.
23-4 Describe the epidemiologies of endocarditis and rheumatic fever.
23-5 Describe the epidemiology of tularemia.
23-6 Describe the epidemiology of brucellosis.
23-7 Describe the epidemiology of anthrax.
23-8 Describe the epidemiology of gas gangrene.
23-9 List three pathogens that are transmitted by animal bites and scratches.
23-10 Compare and contrast the causative agents, vectors, reservoirs, symptoms, treatments, and preventive measures for plague, Lyme disease, and Rocky Mountain spotted fever.
23-11 Identify the vector, etiology, and symptoms of five diseases transmitted by ticks.
23-12 Describe the epidemiologies of epidemic typhus, endemic murine typhus, and spotted fevers.

Once bacteria gain access to the bloodstream, they become widely disseminated. In some cases, they are also able to reproduce rapidly.

Sepsis and Septic Shock

Although blood is normally sterile, moderate numbers of microorganisms can enter the bloodstream without causing harm. In hospital conditions, the blood frequently is contaminated as a result of invasive procedures, such as insertion of catheters and intravenous feeding tubes. Blood and lymph contain numerous defensive phagocytic cells. Also, blood is low in available iron, which is a requirement for bacterial growth. However, if the defenses of the cardiovascular and lymphatic systems fail, microbes can proliferate in the blood. An acute illness that is associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood is termed **septicemia.** A similar term that is not equated medically with septicemia is sepsis, although there is a tendency to use them interchangeably. **Sepsis** is defined as a *systemic inflammatory*



Figure 23.3 Lymphangitis, one sign of sepsis. As the infection spreads from its original site along the lymph vessels, the inflamed walls of the vessels become visible as red streaks.

Q Why does the red streak sometimes end at a certain point?

response syndrome (SIRS) caused by a focus of infection that releases mediators of inflammation into the bloodstream. The site of the infection itself is not necessarily the bloodstream, and in about half of the cases no microbes can be found in the blood. Sepsis and septicemia are often accompanied by the appearance of **lymphangitis,** inflamed lymph vessels visible as red streaks under the skin, running along the arm or leg from the site of the infection (**Figure 23.3**).

If the body's defenses do not quickly control the infection and the resulting SIRS, the results are progressive and frequently fatal. The first stage of this progression is sepsis. The most obvious signs and symptoms are fever, chills, and accelerated breathing and heart rate. When sepsis results in a drop in blood pressure (*shock*) and dysfunction of at least one organ, it is considered to be **severe sepsis.** Once organs begin to fail, the mortality rate becomes very high. A final stage, when low blood pressure can no longer be controlled by addition of fluids, is **septic shock.**

Gram-Negative Sepsis

Septic shock is most likely to be caused by gram-negative bacteria. Recall that the cell walls of many gram-negative bacteria (toxic lipopolysaccharides [LPS]; see page 81) contain endotoxins that are released upon lysis of the cell. These endotoxins can cause a severe drop in blood pressure with its associated signs and symptoms. Septic shock is often called by the alternative names *gram-negative sepsis* or *endotoxic shock.* Less than one-millionth of a milligram of endotoxin is enough to cause the symptoms. About 750,000 cases of septic shock occur each year in the United States; at least 225,000 are fatal.

An effective treatment for severe sepsis and septic shock has been a medical priority for many years. The early symptoms of sepsis are relatively nonspecific and not especially alarming. Therefore, the antibiotic treatments that might arrest it then are frequently not administered. The progression to lethal stages is rapid and generally impossible to treat effectively. Administering antibiotics then may even aggravate the condition by causing the lysis of large numbers of bacteria that then release more endotoxins.

In addition to antibiotics, treatment of septic shock involves attempts to neutralize the LPS components and inflammation-causing cytokines. Attempts to develop an effective drug to do this have been unsuccessful so far.

Gram-Positive Sepsis

Gram-positive bacteria are now the most common cause of sepsis. Both staphylococci and streptococci produce potent exotoxins that cause toxic shock syndrome, a toxemia discussed in Chapter 21 (page 583). The frequent use of invasive procedures in hospitals allows gram-positive bacteria to enter the bloodstream. Such healthcare-associated infections (HAIs) are a particular risk for patients who undergo regular dialysis for kidney dysfunction. The bacterial components that lead to septic shock in gram-positive sepsis are not known with certainty. Possible sources are various fractions of the gram-positive cell wall or even bacterial DNA.

An especially important group of gram-positive bacteria are the enterococci, which are responsible for many HAIs. The enterococci are inhabitants of the human colon and frequently contaminate skin. Once considered relatively harmless, two species in particular, *Enterococcus faecium* and *Enterococcus faecalis,* are now recognized as leading causes of HAIs of wounds and the urinary tract. Enterococci have a natural resistance to penicillin and have rapidly acquired resistance to other antibiotics. What has made them something of a medical emergency is the appearance of vancomycin-resistant strains. Vancomycin (see page 559) was often the only remaining antibiotic to which these bacteria, especially *E. faecium,* were still sensitive. Among isolates of *E. faecium* from HAIs of the bloodstream, almost 90% are now resistant.

Up to this point our discussion of the streptococci has been focused on serologic group A. There is an emerging awareness of **group B streptococci (GBS).** *S. agalactiae* (ā-gal-AK-tē-ī) is the only GBS and is the most common cause of life-threatening *neonatal sepsis.* The Centers for Disease Control and Prevention (CDC) recommends that pregnant women be tested for vaginal GBS and that women with GBS be offered antibiotics during labor.

Puerperal Sepsis

Puerperal sepsis, also called **puerperal fever** and **childbirth fever,** is an HAI. It begins as an infection of the uterus as a result of childbirth or abortion. *Streptococcus pyogenes,* a group

A beta-hemolytic streptococcus, is the most frequent cause, although other organisms may cause infections of this type.

Puerperal sepsis progresses from an infection of the uterus to an infection of the abdominal cavity (*peritonitis*) and in many cases to sepsis. At a Paris hospital between 1861 and 1864, of the 9886 women who gave birth, 1226 (12%) died of such infections. These deaths were largely unnecessary. Some 20 years before, Oliver Wendell Holmes in the United States and Ignaz Semmelweis in Austria had clearly demonstrated that the disease was transmitted by the hands and instruments of the attending midwives or physicians and that disinfecting the hands and instruments could prevent such transmission. Antibiotics, especially penicillin, and modern hygienic practices have now made *S. pyogenes* puerperal sepsis an uncommon complication of childbirth.

Therapy for Sepsis

An effective therapy for sepsis is a medical priority and will probably require entirely new approaches. For one thing, the symptoms of sepsis are largely caused by the body's response to the infection, a response that has been described as being "unhelpfully exuberant." Any agent that would suppress this response would be independent of the source of the infection. Even in the absence of such therapies, the care of patients with sepsis has improved, and the mortality rate in recent years has declined, but is still around 20–25%.

CHECK YOUR UNDERSTANDING

- What are two of the conditions that define the systemic inflammatory response syndrome of sepsis? **23-2**
- Are the endotoxins that cause sepsis from gram-positive or gram-negative bacteria? **23-3**

Bacterial Infections of the Heart

The wall of the heart consists of three layers. The inner layer, called the *endocardium,* lines the heart muscle itself and covers the valves. An inflammation of the endocardium is called **endocarditis.**

One type of bacterial endocarditis, **subacute bacterial endocarditis** (so named because it develops slowly; **Figure 23.4**), is characterized by fever, general weakness, and a heart murmur. It is usually caused by alpha-hemolytic streptococci (most often, *Streptococcus viridans*), which are common in the oral cavity, although enterococci or staphylococci may also be involved. The condition probably arises from a focus of infection elsewhere in the body, such as in the teeth or tonsils. Microorganisms are released by tooth extractions or tonsillectomies, enter the blood, and find their way to the heart. Normally, such bacteria would be quickly cleared from the blood by the body's defensive mechanisms. However, in people whose heart valves are abnormal, because of either congenital heart defects or such diseases as rheumatic fever and syphilis, the bacteria lodge in the

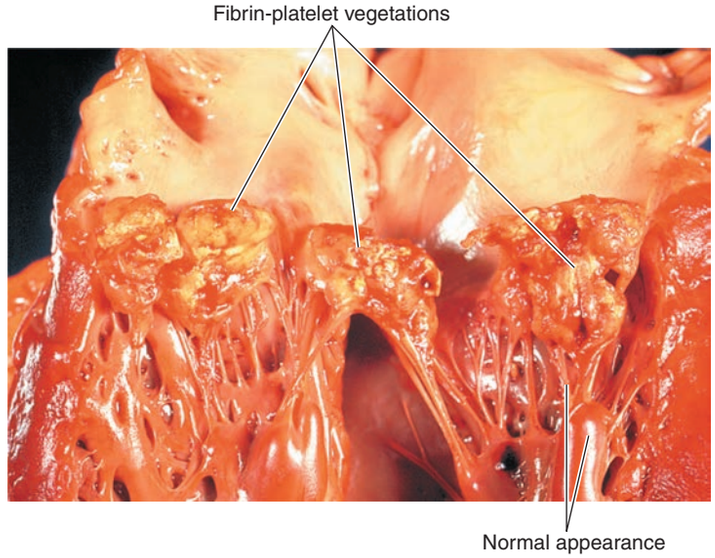


Figure 23.4 Bacterial endocarditis. This is a case of subacute endocarditis, meaning that it developed over a period of weeks or months. The heart has been dissected to expose the mitral valve. The cordlike structures connect the heart valve to the operating muscles.

Q How can a tongue piercing lead to subacute bacterial endocarditis?

preexisting lesions. Within the lesions, the bacteria multiply and become entrapped in blood clots that protect them from phagocytes and antibodies. As multiplication progresses and the clot gets larger, pieces of the clot break off and can block blood vessels or lodge in the kidneys. In time, the function of the heart valves is impaired. Left untreated by appropriate antibiotics, subacute bacterial endocarditis is fatal within a few months.

A more rapidly progressive type of bacterial endocarditis is **acute bacterial endocarditis,** which is usually caused by *Staphylococcus aureus.* The organisms find their way from the initial site of infection to normal or abnormal heart valves; the rapid destruction of the heart valves is frequently fatal within a few days or weeks if untreated. Streptococci can also cause **pericarditis,** inflammation of the sac around the heart (the *pericardium*).

CHECK YOUR UNDERSTANDING

- What medical procedures are usually the cause of endocarditis? **23-4**

Rheumatic Fever

Streptococcal infections, such as those caused by *Streptococcus pyogenes,* sometimes lead to **rheumatic fever,** which is generally considered an autoimmune complication. It occurs primarily in people aged 4 to 18 and often follows an episode of streptococcal sore throat. The disease is usually first expressed as a short period of arthritis and fever. Subcutaneous nodules at

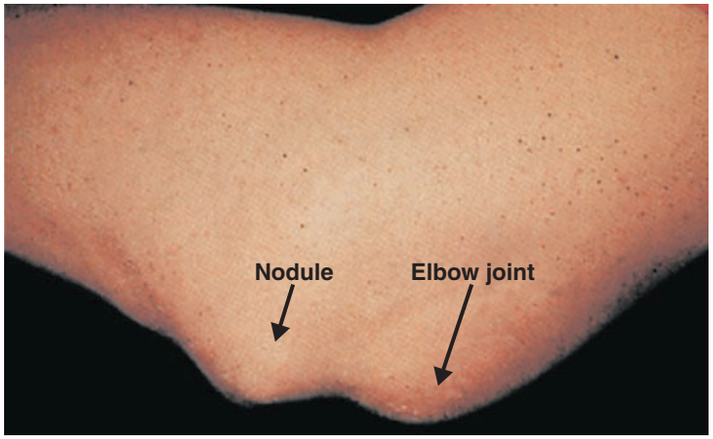


Figure 23.5 A nodule caused by rheumatic fever. Rheumatic fever was named, in part, because of the characteristic subcutaneous nodules that appear at the joints, as shown in this patient's elbow. Infection with group A beta-hemolytic streptococci sometimes leads to this autoimmune complication.

Q Is rheumatic fever a bacterial infection?

joints often accompany this stage (Figure 23.5). In about half of persons affected, an inflammation of the heart, probably from a misdirected immune reaction against streptococcal M protein, damages the valves. Reinfection with streptococci renews the immune attack. Damage to heart valves may be serious enough to result in eventual failure and death. People who have had an episode of rheumatic fever are at risk of renewed immunological damage with repeated streptococcal sore throats. The bacteria have remained sensitive to penicillin, and patients at particular risk, such as these, often receive a monthly preventive injection of long-acting penicillin G benzathine.

As many as 10% of people with rheumatic fever develop **Sydenham's chorea,** an unusual complication known in the Middle Ages as Saint Vitus' dance. Several months following an episode of rheumatic fever, the patient (much more likely to be a girl than a boy) exhibits purposeless, involuntary movements during waking hours. Occasionally, sedation is required to prevent self-injury from flailing arms and legs. The condition disappears after a few months.

Sepsis and infections of the heart are summarized in Diseases in Focus 23.1.

Tularemia

Tularemia is an example of a *zoonotic* disease, that is, a disease transmitted by contact with infected animals, in this case most commonly rabbits and ground squirrels. The name derives from Tulare County, California, where the disease was originally observed in ground squirrels in 1911. The pathogen is *Francisella tularensis,* a small gram-negative bacillus. It can enter humans by several routes. The most common is penetration of the skin at a minor abrasion, where it creates an ulcer at the site. About a week after infection, the regional lymph nodes enlarge; many will contain pockets of pus. (See the Clinical Focus box on page 645.) The bacterium can multiply in macrophages—as much as a thousand-fold. Mortality is normally less than 3%. If left untreated, the proliferation of *F. tularensis* can lead to sepsis and infection of multiple organs.

Almost 90% of cases in the United States are related to contact with rabbits, and the disease is often known locally as *rabbit fever.* Tularemia is also transmitted in some areas by ticks and insects and is known there as *deer fly fever.* Respiratory infection, usually by dust contaminated by urine or feces of infected animals, can cause an acute pneumonia with a mortality rate exceeding 30%. The infective dose is very small, and handling this organism requires biosafety level 3 procedures (see page 160).

At one time, so few cases of tularemia (fewer than 200) were recorded annually in the United States that it was removed from the list of nationally notifiable diseases, However, concern that it might be used as a biological weapon has recently led to its reinstatement on the list. Figure 23.6 illustrates the geographic distribution of tularemia within the United States. It is also found worldwide in many areas of the Northern Hemisphere.

The intracellular location of the bacterium is a problem in chemotherapy. Antibiotics such as tetracycline, administered for 10 to 15 days, are an effective treatment.

CHECK YOUR UNDERSTANDING

What animals are the most common reservoir for tularemia? **23-5**

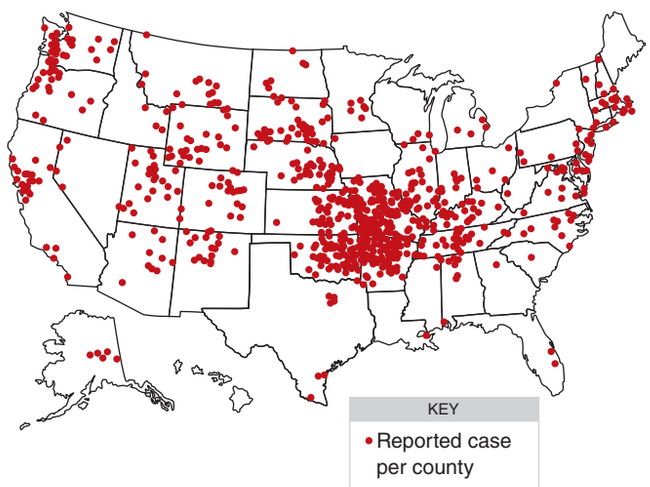


Figure 23.6 Tularemia cases in the United States (2001–2010). There were 1133 cases for which a county of residence was reported. Each dot represents a case.

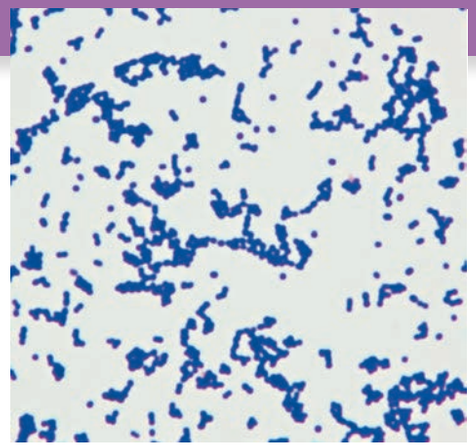
Source: CDC *MMWR* 62(47): 963–966, November 29, 2013.

Q What area reporting tularemia is closest to you?

DISEASES IN FOCUS 23.1

Human-reservoir Infections

Differential diagnosis is the process of identifying a disease by examining a patient and comparing the results to a list of possible diseases. A differential diagnosis is important for providing initial treatment and for laboratory testing. Microorganisms circulating in the blood may reflect a serious, uncontrolled infection. For example, a 27-year-old woman has a fever and cough for 5 days. She is hospitalized when her blood pressure drops. Despite aggressive treatment with fluids and massive doses of antibiotics, she dies 5 hours after hospitalization. Catalase-negative, gram-positive cocci are isolated from her blood. Use the table below to provide a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Gram-positive cocci. LM 5 μm

Disease	Pathogen	Symptoms	Reservoir	Method of Transmission	Treatment
BACTERIAL DISEASES					
Septic Shock	Gram-negative bacteria, enterococci, group B streptococci	Fever, chills, increased heart rate; lymphangitis	Human body	Injection; catheterization	Antibiotics
Puerperal Sepsis	*Streptococcus pyogenes*	Peritonitis; sepsis	Human nasopharynx	Nosocomial	Penicillin
Endocarditis **Subacute Bacterial** **Acute Bacterial**	Mostly alpha-hemolytic streptococci; *Staphylococcus aureus*	Fever, general weakness, heart murmur; damage to heart valves	Human nasopharynx	From focal infection	Antibiotics
Pericarditis	*Streptococcus pyogenes*	Fever; general weakness; heart murmur	Human nasopharynx	From focal infection	Antibiotics
Rheumatic Fever	Group A beta-hemolytic streptococci	Arthritis, fever; damage to heart valves	Immune reactions to streptococcal infections	Not transmissible	Supportive. Prevention: penicillin to treat streptococcal sore throats
VIRAL DISEASES					
Burkitt's Lymphoma	Epstein-Barr (EB) virus	Tumor	Unknown	Unknown	Surgery
Infectious Mononucleosis	EB virus	Fever, general weakness	Humans	Saliva	None
Cytomegalovirus	Cytomegalovirus	Mostly asymptomatic; initial infection acquired during pregnancy can be damaging to fetus	Humans	Body fluids	Ganciclovir, fomivirsen
UNKNOWN ETIOLOGY					
Kawasaki Syndrome	Unknown	Fever, rash, coronary artery abnormalities	Unknown	Unknown	None

Brucellosis (Undulant Fever)

With over 500,000 new human cases annually, **brucellosis** is the world's most common bacterial zoonosis. The Middle East is an endemic area, and several countries in the region record the world's highest incidence of the disease. It is widespread around the Mediterranean and in southeastern Europe, Asia, Latin America, and the Caribbean. It is also economically important as a disease of animals in the developing world. Human cases of brucellosis are usually not fatal, but the disease tends to persist in the reticuloendothelial system (see page 649), where the bacteria evade the host's defenses; they are especially adept at evading phagocytic cells. This ability allows long-term survival and replication. The disease often becomes chronic and is capable of affecting any organ system.

Brucella bacteria are small, aerobic, gram-negative coccoid rods. During laboratory handling, they easily become airborne and are considered dangerous to handle. In fact, they are considered a potential agent of bioterrorism. There are three species of *Brucella* bacteria that are of greatest interest. *Brucella abortus* (broo-SEL-lah ah-BOR-tus) is found primarily in cattle but also infects camels, bison, and several other animals. *Brucella suis* (SOO-is) is a species mostly infecting swine but is known to infect cattle when they are kept in contact with swine herds. Abattoir (slaughterhouse) workers who come in contact with swine carcasses are at risk of brucellosis from this species. The most serious pathogen, and the cause of most human cases, is *Brucella melitensis* (mel-i-TEN-sis). This species is most commonly found today in goats and sheep.

At the present time, most cases of brucellosis are caused by *B. melitensis,* predominantly among Hispanics. The disease is endemic in Mexico and is often imported into the United States in unpasteurized food products, such as Mexican soft cheese made from goat milk.

The incubation period is usually 1 to 3 weeks but might be much longer. Symptoms of brucellosis have a wide spectrum, depending on the stage of the disease and the organs affected. Typically they include fever (often rising and falling, which has given the disease an alternative name of *undulant fever*), malaise, night sweats, and muscle aches. Although several serological tests are available, there is still a need for a definitive diagnostic test. The ultimate diagnostic proof is isolation of *Brucella* from the patient's blood or tissue. Because the disease is not common, diagnosis often must start with patient interviews that suggest a contact in endemic areas of the disease.

Antibiotic therapy is possible, and the bacteria have not shown development of resistance. However, treatment must be very long term, usually at least 6 weeks, and involves a combination of at least two antibiotics.

CHECK YOUR UNDERSTANDING

What ethnic group in the United States is most commonly affected by brucellosis, and why? **23-6**

Anthrax

In 1877, Robert Koch isolated *Bacillus anthracis,* the bacterium that causes **anthrax** in animals. The endospore-forming bacillus is a large, aerobic, gram-positive microorganism that is apparently able to grow slowly in soil types that meet specific moisture conditions. The endospores have survived in soil tests for up to 60 years. The disease strikes primarily grazing mammals, such as cattle and sheep. The *B. anthracis* endospores are ingested along with grasses, causing a fulminating, fatal sepsis.

The incidence of human anthrax is now rare in the United States. People at risk are those who handle animals, hides, wool, and other animal products from certain foreign countries. (See the Clinical Case, Chapter 2.)

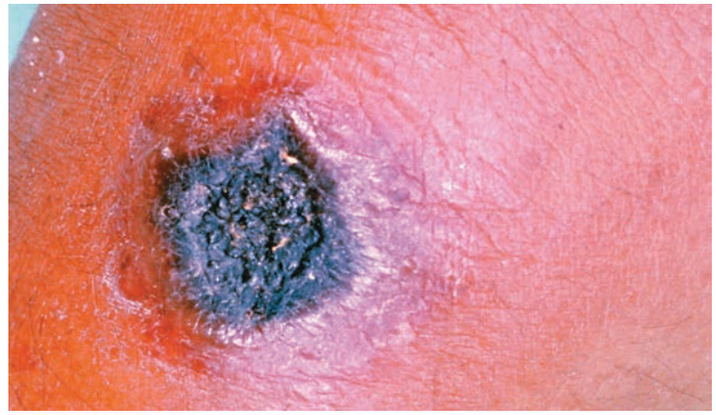


Figure 23.7 Anthrax lesion. The swelling and formation of a black scab that forms around the point of infection is a characteristic of cutaneous anthrax.

What are the other types of anthrax?

Infections by *B. anthracis* are initiated by endospores. Once introduced into the body, they are taken up by macrophages, where they germinate into vegetative cells. These are not killed, but multiply, eventually killing the macrophage. The released bacteria then enter the bloodstream, replicate rapidly, and secrete toxins.

The primary virulence factors of *B. anthracis* are two exotoxins. Both toxins share a third toxic component, a cell receptor–binding protein called the *protective antigen,* that binds the toxins to target cells and permits their entry. One toxin, the *edema toxin,* causes local edema (swelling) and interferes with phagocytosis by macrophages. The other toxin, *lethal toxin,* specifically targets and kills macrophages, which disables an essential defense of the host. Furthermore, the capsule of *B. anthracis* is very unusual. It is not a polysaccharide but rather is composed of amino acid residues, which for some reason do not stimulate a protective response by the immune system. Therefore, once the anthrax bacteria enter the bloodstream, they proliferate without any effective inhibition until there are tens of millions per milliliter. These immense populations of toxin-secreting bacteria ultimately kill the host.

Anthrax affects humans in three forms: cutaneous anthrax, gastrointestinal anthrax, and inhalational (pulmonary) anthrax.

Cutaneous anthrax results from contact with material containing anthrax endospores. Over 90% of naturally occurring cases of anthrax in humans are cutaneous; the endospore enters at some minor skin lesion. A papule appears and then eventually vesicles, which rupture and form a depressed, ulcerated area that is covered by a black eschar (scab) as shown in **Figure 23.7**. (The name *anthrax* is derived from the Greek word for coal.) In most cases the pathogen does not enter the bloodstream, and other symptoms are limited to a low-grade fever and malaise. However, if the bacteria enter the bloodstream, mortality without antibiotic

CLINICAL FOCUS

A Sick Child

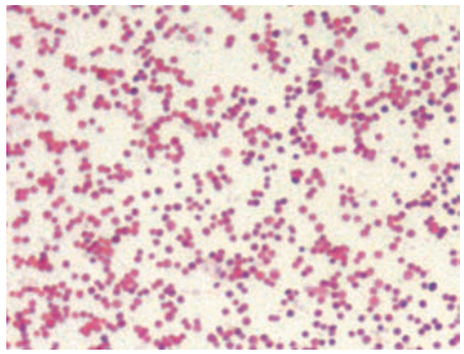
As you read through this problem, you will encounter questions that primary health care providers ask themselves as they solve a clinical problem. Try to answer each question as a health care provider.

1. On February 15, Tyler, a 3-year-old boy, is seen by his pediatrician for fever, malaise, painful left underarm lymph node, and skin sloughing off his left ring finger. Amoxicillin is prescribed.
   What diseases are possible?
2. Intermittent fever and enlarged lymph node persist for 49 days. Tyler then undergoes excisional biopsy of the left axillary lymph node. The excised tissue is cultured; a Gram stain of the bacteria that grew is shown in the figure.
   What additional tests would you do?
3. Serological tests revealed the following results:

Pathogen	Antibody Titer
Bartonella	0
Ehrlichia	0
Francisella	4,096
Cytomegalovirus	0
Toxoplasma gondii	0

Tyler improves after treatment with ciprofloxacin.
What is the cause of the infection? What do you need to know?

4. PCR is used to confirm identification of *Francisella tularensis*. Between January 2 and February 8, Tyler's family purchased six hamsters from a pet store. Each hamster died from diarrhea within one week of purchase. One hamster bit the child on the left ring finger.
   Where will you look for the source of the infection?
5. Workers at the pet store report an unusual number of deaths among hamsters but not other animals during January and February. Eight other customers report that their hamsters died within 2 weeks of purchase. Available hamsters are negative for *F. tularensis* by serology and culture. One of two cats kept as store pets have a positive serologic test for *F. tularenesis* at a titer of 256. The hamsters came from customers who had pets with unanticipated litters.
   What is the most likely source of infection?
6. The hamsters came from different sources, so they are probably not the origin of the infection. The positive serological test in a pet cat suggests that infected wild rodents infested the store and spread the infection to hamsters by urinating and defecating through the hamster cages. The infected cat might have had an unrecognized illness after catching or eating an infected wild rodent.



Gram-stained bacteria cultured from lymph node. LM 2 μm

Public health officials should be aware that pet rodents might be a source of tularemia. Identifying the organism is important because it is often resistant to antibiotics commonly used for skin and systemic infections and because it is a potential agent of biological terrorism.

Source: Adapted from *MMWR* 53(52): 1202, January 7, 2005 and *MMWR* 62(47): 963–966, November 29, 2013.

treatment can reach 20%; with antibiotic therapy, mortality is usually less than 1%.

A relatively rare form of anthrax is **gastrointestinal anthrax** caused by ingestion of undercooked food containing anthrax endospores. Symptoms are nausea, abdominal pain, and bloody diarrhea. Ulcerative lesions occur in the gastrointestinal tract ranging from the mouth and throat to, mainly, the intestines. Mortality is usually more than 50%.

The most dangerous form of anthrax in humans is **inhalational (pulmonary) anthrax.** Endospores inhaled into the lungs have a high probability of entering the bloodstream. Symptoms of the first few days of the infection are not especially alarming: mild fever, coughing, and some chest pain. Antibiotics can arrest the disease at this stage, but unless suspicion of anthrax is high, they are unlikely to be administered. As the bacteria enter the bloodstream and proliferate, the illness progresses in 2 or 3 days into septic shock that usually kills the patient within 24 to 36 hours. The mortality rate is exceptionally high, approaching 100%.

Antibiotics are effective in treating anthrax if they are administered in time. Currently recommended drugs are ciprofloxacin or doxycycline plus one or two additional agents that are known to be active against the pathogen. A recent development in the treatment of symptomatic inhalational anthrax is the use of raxibacumab, which inhibits the formation of toxin. This monoclonal antibody has proven to be effective in animal studies. People who have been exposed to anthrax endospores can be given preventive doses of antibiotics for a time as a precaution. This time period is usually quite long because experience has shown that up to 60 days can elapse before the inhaled endospores germinate and initiate active disease.

Vaccination of livestock against anthrax is a standard procedure in endemic areas. A single dose of an effective live, attenuated vaccine is used, which is considered unsafe for use in humans. The only vaccine currently approved for use in humans contains an inactivated form of the protective antigen toxin and



Figure 23.8 The toes of a patient with gangrene. This disease is caused by *Clostridium perfringens* and other clostridia. The black, necrotic tissue, resulting from poor circulation or injury, furnishes anaerobic growth conditions for the bacteria, which then progressively destroy adjoining tissue.

Q How can gangrene be prevented?

is designed to prevent entry of the other two toxins into the host's cells. This vaccine requires a series of six injections over a period of 18 months, followed by annual boosters. In view of the recent use of anthrax as a weapon of bioterrorism (see the Applications of Microbiology box on page 648), the need for a more practical human vaccine has become urgent. The goal is a vaccine that would require no more than three injections and would work rapidly enough that it could be given *after* exposure to anthrax endospores.

Diagnosis of anthrax has usually consisted of isolation and identification of *B. anthracis* from a clinical specimen—which is too slow for detection of bioterrorism outbreaks. A blood test can detect both inhalational and cutaneous cases of anthrax within an hour. Furthermore, locations such as a few mail-sorting facilities are being equipped with automated electronic sensors that can immediately detect anthrax spores.

CHECK YOUR UNDERSTANDING

✓ How do animals such as cattle become victims of anthrax? **23-7**

Gangrene

If a wound causes the blood supply to be interrupted, a condition known as **ischemia,** the wound becomes anaerobic. Ischemia leads to **necrosis,** or tissue death. The death of soft tissue resulting from the loss of blood supply is called **gangrene** (Figure 23.8). These conditions can also occur as a complication of diabetes.

Substances released from dying and dead cells provide nutrients for many bacteria. Various species of the genus *Clostridium,* which are gram-positive, endospore-forming anaerobes widely found in soil and in the intestinal tracts of humans and domesticated animals, grow readily in such conditions. *C. perfringens* is the species most commonly involved in gangrene, but other clostridia and several other bacteria can also grow in such wounds.

Once ischemia and the subsequent necrosis caused by impaired blood supply have developed, **gas gangrene** can develop, especially in muscle tissue. As the *C. perfringens* microorganisms grow, they ferment carbohydrates in the tissue and produce gases (carbon dioxide and hydrogen) that swell the tissue. The bacteria produce toxins that move along muscle bundles, killing cells and producing necrotic tissue that is favorable for further bacterial growth. Eventually, these toxins and bacteria enter the bloodstream and cause systemic illness. Enzymes produced by the bacteria degrade collagen and proteinaceous tissue, facilitating the spread of the disease. Without treatment, the condition is fatal.

Gas gangrene can also result from improperly performed abortions. *C. perfringens,* which resides in the genital tract of about 5% of all women, can infect the uterine wall and lead to gas gangrene, resulting in a life-threatening bloodstream infection.

The surgical removal of necrotic tissue and amputation are the most common medical treatments for gas gangrene. When gas gangrene occurs in such regions as the abdominal cavity or the reproductive tract, the patient can be treated in a **hyperbaric chamber,** which contains a pressurized oxygen-rich atmosphere. The oxygen saturates the infected tissues and thereby prevents the growth of the obligately anaerobic clostridia. Small chambers are available that can accommodate a gangrenous limb. The prompt cleaning of serious wounds and precautionary treatment with penicillin are the most effective steps in preventing gas gangrene.

CHECK YOUR UNDERSTANDING

✓ Why are hyperbaric chambers effective in treating gas gangrene? **23-8**

Systemic Diseases Caused by Bites and Scratches

Animal bites can result in serious infections. About 4.4 million animal bites occur in the United States annually, accounting for about 1% of visits to the emergency rooms in hospitals.

Dog bites make up at least 80% of reported bite incidents; cat bites, only about 10%. Cat bites are, however, more penetrating, resulting in a higher infection rate (30–50%) than the bites of dogs (15–20%). Domestic animals often harbor *Pasteurella multocida* (PAS-tyer-el-lah MUL-tō-si-dah), a gram-negative rod similar to the *Yersinia* bacterium that causes plague (page 647). *P. multocida* is primarily a pathogen of animals, and it causes sepsis (hence the name *multocida,* meaning many-killing).

Humans infected with *P. multocida* have varied responses. For example, local infections with severe swelling and pain can develop at the site of the wound. Forms of pneumonia and

sepsis may develop and are life-threatening. Penicillin and tetracycline are usually effective in treating these infections.

In addition to *P. multocida,* an assortment of anaerobic bacterial species are often found in infected animal bites, as well as species of *Staphylococcus, Streptococcus,* and *Corynebacterium.* Bites by humans, mostly as a result of fighting, are also prone to serious infections. In fact, before antibiotic therapy became available, nearly 20% of victims of human bites on extremities required amputation—currently only about 5% of cases require it.

Cat-Scratch Disease

Cat-scratch disease, although it receives little attention, is surprisingly common. An estimated 22,000 or more cases occur annually in the United States, many more than the well-known Lyme disease. People who own or are closely exposed to cats are at risk. The pathogen is an aerobic, gram-negative bacterium, *Bartonella henselae* (BAR-tō-nel-lah HEN-sel-ī). Microscopy shows that the bacterium can inhabit the interior of some cat red blood cells. It is connected to the exterior of the cell and to the surrounding extracellular fluid by a pore (**Figure 23.9**). Resident there, the bacteria cause a persistent bacteremia in cats; it is estimated that as many as 50% of domestic and feral (wild) cats carry these bacteria in their blood. The primary mode of transmission is by the scratch of a cat; it is uncertain whether bites of cats or of cat fleas transmit the disease to humans. But the presence of cat fleas is definitely a requirement for the infection to be maintained among cats. *B. henselae* multiplies in the digestive system of the cat flea and survives for several days in flea feces. Cat claws then become contaminated from flea feces.

The initial sign is a papule at the infection site, which appears 3 to 10 days after exposure. Swelling of the lymph nodes and usually malaise and fever follow in a couple of weeks. Cat-scratch disease is ordinarily self-limiting, with a duration of a few weeks, but in severe cases antibiotic therapy may be effective.

Rat-Bite Fever

In large urban areas (even in the United States), the rat population is not well controlled, and bites from rats are a fairly common occurrence—and may cause the disease **rat-bite fever.** At one time, the victims of rat bites were small children in substandard housing. Today, rats are popular as laboratory study animals and even as pets; potential patients are now often laboratory technicians who handle rats as well as pet owners and pet store workers. Although about half of both wild and laboratory rats are known to carry the bacterial pathogens, only a minority of rat bites (about 10%) result in disease.

There are two similar but distinct diseases. In North America the more common disease, called *streptobacillary rat-bite fever,* is caused by *Streptobacillus moniliformis* (when the pathogen is ingested, the disease is termed *Haverhill fever*). This is a filamentous, gram-negative, highly pleomorphic, fastidious bacterium that is difficult to culture, although isolation in culture

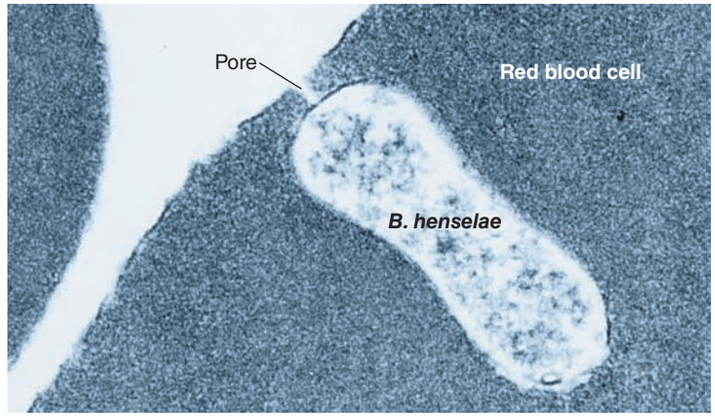


Figure 23.9 Electron micrograph showing the location of *Bartonella henselae* within a red blood cell. Only a pore connects the bacterium with the extracellular fluid.

Q Why can *B. henselae* infection persist in cats?

is the best diagnostic method. The symptoms are initially fever, chills, and muscle and joint pain, followed in a few days by a rash on the extremities. Occasionally there are more serious complications; if untreated, mortality is around 10%.

The other bacterial pathogen causing rat-bite fever is *Spirillum minus.* In this case, the disease is called *spirillar fever;* in Asia, where most cases occur, it is known as *sodoku.* It is more likely to occur in bites by wild rodents. The symptoms are similar to those of streptobacillary rat-bite fever. Because the pathogen cannot be cultured, diagnosis is made by microscopic observation of the gram-negative, spiral-shaped bacterium. Treatment by penicillin or doxycycline is usually effective for both forms of rat-bite fever.

Cardiovascular infections transmitted to humans by contact with other animals are summarized in Diseases in Focus 23.2.

CHECK YOUR UNDERSTANDING

✓ *Bartonella henselae,* the pathogen of cat-scratch disease, is capable of growth in what insect? **23-9**

Vector-Transmitted Diseases

Vector-borne diseases of the cardiovascular system are summarized in Diseases in Focus 23.3. See pages 658–659 for the **Big Picture** box on how climate change is impacting the vector for chikungunya fever, a disease discussed later in the chapter.

Plague

Few diseases have affected human history more dramatically than **plague,** known in the Middle Ages as the Black Death. This term comes from one of its characteristics, the dark blue areas of skin caused by hemorrhages.

Protection against Bioterrorism

The idea of biological weapons, or bioweapons—that is, the use of living pathogens for hostile purposes—is not new. The earliest recorded use of biological warfare occurred in 1346. The Tartar army catapulted plague-ridden bodies over the walls of Kaffa (Ukraine). After the fall of Kaffa, survivors escaping the fallen city introduced plague into Europe. Thus began the plague pandemic of 1348–1350. During the Sino-Japanese War (1937–1945), airplanes dropped canisters of fleas carrying *Yersinia pestis* on China.

In 1979, *Bacillus anthracis* was being produced in Sverdlovsk (Soviet Union) when an accidental release of *B. anthracis* resulted in 100 deaths in a 2-week period.

Historically, biological weapons have been associated with military action. The use of biological agents to intimidate civilians and governments, **bioterrorism,** began late in the twentieth century.

- In 1984, a religious cult attacked the people of The Dalles, Oregon, by intentionally contaminating food in restaurants and supermarkets with *Salmonella enterica.*
- In 1996, 15 people developed severe gastroenteritis requiring hospitalization when a laboratory worker intentionally contaminated pastries with *Shigella dysenteriae.*
- In 2001, five people died when an Army researcher used the U.S. Postal Service to spread *Bacillus anthracis* in New York City and Washington, D.C.

One of the problems with bioweapons is that they contain living organisms (see the table), so their impact is difficult to control or even predict. When the use of biological agents is considered a possibility, military personnel and first-responders (health care personnel and others) are vaccinated if a vaccine for the suspected agent exists. The current plan to protect civilians in the event of an attack with a microbe is illustrated by the smallpox preparedness plan. It is not practical to vaccinate everyone against smallpox. The U.S. government's current strategy following a confirmed smallpox outbreak includes "ring containment and voluntary vaccination." Ring containment consists of identifying people with the infection, vaccinating everyone who has had contact with them, and then vaccinating people in surrounding areas.



The bioweapons detector called Canary uses B cells specific to a particular bacterium or virus. The B cells are genetically modified to emit light when they detect their target pathogen.

It might not be possible to stop all wars, but the public health system is improving its ability to respond to bioweapons. Rapid tests to detect genetic changes in hosts due to bioweapons even before symptoms develop are being investigated. Early warning systems, such as DNA chips or recombinant cells that fluoresce (see the figure) in the presence of a bioweapon, are being developed. New vaccines are being developed, and existing vaccines are being stockpiled for use where needed.

The "ideal" bioweapon is one that is disseminated by aerosol, is spread efficiently from human to human, causes a debilitating disease, and has no readily available treatment. Lists of potential biological weapons usually contain organisms listed below.

Bacteria	Viruses
Bacillus anthracis	Arenaviruses
Brucella spp.	Hantavirus, encephalitis viruses
Chlamydophila psittaci	Hemorrhagic fever viruses (Ebola, Marburg, Lassa)
Clostridium botulinum toxin	Monkeypox
Coxiella burnetii	Nipah virus
Francisella tularensis	Smallpox
Rickettsia prowazekii	
Shigella spp.	
Vibrio cholerae	
Yersinia pestis	

The disease is caused by a gram-negative, rod-shaped bacterium, *Yersinia pestis.* Normally a disease of rats, plague is transmitted from one rat to another by the rat flea, *Xenopsylla cheopis* (zē-NOP-sil-lah chē-Ō-pis) (see Figure 12.32b, page 352). In the far West and Southwest, the disease is endemic in wild rodents, especially ground squirrels and prairie dogs.

If its host dies, the flea seeks a replacement host, which may be another rodent or a human. It can jump about 3.5 inches. A plague-infected flea is hungry for a meal because the growth of the bacteria forms a biofilm that blocks the flea's digestive tract, and the blood the flea ingests is quickly regurgitated. An arthropod vector is not always necessary for plague transmission. Contact from the skinning of infected animals; scratches, bites,

DISEASES IN FOCUS 23.2

Infections from Animal Reservoirs Transmitted by Direct Contact

The following diseases should be included in the differential diagnosis of patients with exposure to animals. A 10-year-old girl is admitted to a local hospital after having a fever (40°C) for 12 days and back pain for 8 days. Bacteria cannot be cultured from tissues. She has a recent history of dog and cat scratches. She recovers without treatment. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



The patient's infected scratch.

Disease	Pathogen	Symptoms	Reservoir	Method of Transmission	Treatment
BACTERIAL DISEASES					
Brucellosis	*Brucella* spp.	Local abscess; undulating fever	Grazing mammals	Direct contact	Tetracycline, streptomycin
Anthrax	*Bacillus anthracis*	Papule (cutaneous); bloody diarrhea (gastrointestinal); septic shock (inhalational)	Soil; large grazing mammals	Direct contact; ingestion; inhalation	Ciprofloxacin; doxycycline
Animal Bites	*Pasteurella multocida*	Local infection; sepsis	Animal mouths	Dog/cat bites	Penicillin
Rat-Bite Fever	*Streptobacillus moniliformis, Spirillum minus*	Sepsis	Rats	Rat bites	Penicillin
Cat-Scratch Disease	*Bartonella henselae*	Prolonged fever	Domestic cats	Cat bites or scratches, fleas	Antibiotics
PROTOZOAN DISEASE					
Toxoplasmosis	*Toxoplasma gondii*	Mild disease; initial infection acquired during pregnancy can be damaging to fetus; serious illness in AIDS patients	Domestic cats	Ingestion	Pyrimethamine, sulfadiazine and folinic acid

and licks by domestic cats; and similar incidents have been reported to cause infection.

In the United States, exposure to plague is increasing, as residential areas encroach on areas with infected animals. In parts of the world where human proximity to rats is common, infection from this source still prevails.

From the flea bite, bacteria enter the human's bloodstream and proliferate in the lymph and blood. One factor in the virulence of the plague bacterium is its ability to survive and proliferate inside phagocytic cells rather than being destroyed by them. An increased number of highly virulent organisms eventually emerges, and an overwhelming infection results. The lymph nodes in the groin and armpit become enlarged, and fever develops as the body's defenses react to the infection. Such swellings, called *buboes,* account for the name **bubonic plague** (Figure 23.10). This is the most common form, comprising 80–95% of cases today. The mortality rate of untreated bubonic plague is 50–75%. Death, if it occurs, is usually within less than a week after the appearance of symptoms.



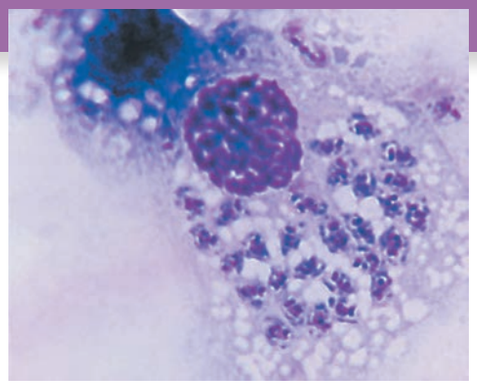
Figure 23.10 A case of bubonic plague. Bubonic plague is caused by infection with *Yersinia pestis*. This photograph shows a bubo (swollen lymph node) on the thigh of a patient. Swollen lymph nodes are a common indication of systemic infection.

Q In what two ways is plague transmitted?

DISEASES IN FOCUS 23.3

Infections Transmitted by Vectors

The following diseases should be considered in the differential diagnosis of patients with a history of tick and insect bites or who have traveled to endemic countries. These diseases are all prevented by controlling exposure to insect and tick bites. A 22-year-old soldier returning from a tour of duty in Iraq has three painless skin ulcers. She reports being bitten by insects every night. Ovoid, protozoa-like bodies are observed within her macrophages by examination with a light microscope. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



A macrophage almost entirely filled with ovoid cells. LM 5 μm

Disease	Pathogen	Symptoms	Reservoir	Method of Transmission	Treatment
BACTERIAL DISEASES					
Tularemia	*Francisella tularensis*	Local infection; pneumonia	Rabbits; ground squirrels	Direct contact with infected animals, deer fly bite; inhalation	Tetracycline
Plague	*Yersinia pestis*	Enlarged lymph nodes; septic shock	Rodents	Fleas; inhalation	Streptomycin; tetracycline
Relapsing Fever	*Borrelia* spp.	Series of fever peaks	Rodents	Soft ticks	Tetracycline
Lyme Disease	*Borrelia burgdorferi*	Bull's-eye rash; neurologic symptoms	Field mice	*Ixodes* ticks	Antibiotics
Ehrlichiosis and Anaplasmosis	*Ehrlichia* spp. *Anaplasma* spp.	Flulike	Deer	*Ixodes* ticks	Tetracycline
Typhus Fever	*Rickettsia prowazekii*	High fever, stupor, rash	Squirrels	*Pediculus humanus corporis* louse	Tetracycline; chloramphenicol
Endemic Murine Typhus	*Rickettsia typhi*	Fever; rash	Rodents	*Xenopsylla cheopis* flea	Tetracycline; chloramphenicol
Rocky Mountain Spotted Fever	*Rickettsia rickettsii*	Macular rash; fever; headache	Ticks; small mammals	*Dermacentor* ticks	Tetracycline, chloramphenicol
VIRAL DISEASE					
Chikungunya Fever	Chikungunya virus	Fever; joint pain	Humans	*Aedes* mosquito	Supportive
PROTOZOAN DISEASES					
Chagas' Disease (American Trypanosomiasis)	*Trypanosoma cruzi*	Damage to heart muscle or peristaltic movement of gastrointestinal tract	Rodents, opossums	Reduviid bug	Nifurtimox
Malaria	*Plasmodium* spp.	Fever and chills at intervals	Humans	*Anopheles* mosquito	Malarone, artemisinin
Leishmaniasis	*Leishmania* spp.	*L. donovani:* systemic disease; *L. tropica:* skin sores; *L. braziliensis:* disfiguring damage to mucous membranes	Small mammals	Sandfly	Antimony compounds
Babesiosis	*Babesia microti*	Fever and chills at intervals	Rodents	*Ixodes* ticks	Atovaquone and azithromycin

A particularly dangerous condition called **septicemic plague** arises when the bacteria enter the blood and proliferate, causing septic shock. Eventually, the blood carries the bacteria to the lungs, and a form of the disease called **pneumonic plague** results. The mortality rate for this type of plague is nearly 100%. Even today, this disease can rarely be controlled if it isn't recognized within 12 to 15 hours of the onset of fever.

Pneumonic plague is easily spread by airborne droplets from humans or animals. Great care must be taken to prevent airborne infection of people in contact with patients.

Europe was ravaged by repeated pandemics of plague; from the years 542 to 767, outbreaks occurred repeatedly in cycles of a few years. After a lapse of centuries, the disease reappeared in devastating form in the fourteenth and fifteenth centuries. It is estimated to have killed more than 25% of the population, resulting in lasting effects on the social and economic structure of Europe. A nineteenth-century pandemic primarily affected Asiatic countries; 12 million are estimated to have died in India. The last major rat-associated urban outbreak in the United States occurred in Los Angeles in 1924 and 1925. Following this, the disease became a rarity until it reappeared in 1965 on the Navajo reservation in the Southwest. Plague, once established in the ground squirrel and prairie dog communities in this area, has gradually spread over much of the western states (**Figure 23.11**). A peak incidence of 40 cases occurred in 1983. A few cases have also arisen from cats, a new animal reservoir, and one from urban tree squirrels.

Plague has been most commonly diagnosed by isolating the bacterium and then sending it to a laboratory for identification. A rapid diagnostic test, however, can reliably detect the presence of the capsular antigen of *Y. pestis* in blood and other fluids of patients within 15 minutes even under remote field conditions. People exposed to infection can be given prophylactic antibiotic protection. A number of antibiotics, including streptomycin and tetracycline, are effective. Recovery from the disease confers reliable immunity. A vaccine is available for people likely to come into contact with infected fleas during field operations or for laboratory workers exposed to the pathogen.

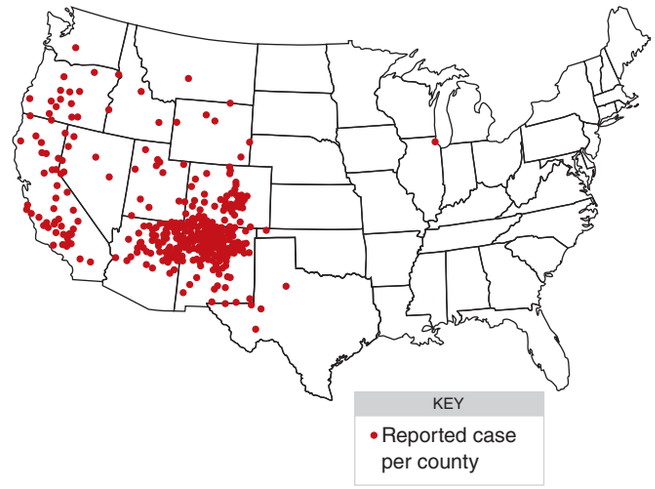


Figure 23.11 The U.S. geographic distribution of human plague, 1970–2012.

Source: CDC, 2013.

Q What area reporting plague is closest to you?

Relapsing Fever

Except for the species that causes Lyme disease (discussed below), all members of the spirochete genus *Borrelia* cause **relapsing fever.** In the United States, the disease is transmitted by soft ticks that feed on rodents. The incidence of relapsing fever increases during the summer months, when the activity of rodents and arthropods increases.

The disease is characterized by fever, sometimes in excess of 40.5°C, jaundice, and rose-colored skin spots. After 3 to 5 days, the fever subsides. Three or four relapses may occur, each shorter and less severe than the initial fever. Each recurrence is caused by a different antigenic type of the spirochete, which evades existing immunity. Diagnosis is made by observing the bacteria in the patient's blood, which is unusual for a spirochete disease. Tetracycline is effective for treatment.

Lyme Disease (Lyme Borreliosis)

In 1975, a cluster of disease cases in young people that was first diagnosed as rheumatoid arthritis was reported near the city of Lyme, Connecticut. The seasonal occurrence (summer months), lack of contagiousness among family members, and descriptions of an unusual skin rash that appeared several weeks before the first symptoms suggested a tickborne disease. In 1983, a spirochete that was later named *Borrelia burgdorferi* was identified as the cause. **Lyme disease** may now be the most common tickborne disease in the United States. In Europe and Asia, the disease is usually known as **Lyme borreliosis.** Often, in these locales the tick and *Borrelia* species differ from those in the United States. Tens of thousands of cases are reported annually. In the United States, Lyme disease is most prevalent on the Atlantic coast (**Figure 23.12**).

Field mice are the most important animal reservoir. The nymphal stage of the tick feeds on infected mice and is the most likely to infect humans, even though adult ticks are about twice as likely to carry the bacterial pathogen. This is because nymphal ticks are small and less likely to be noticed before the infection is transmitted. Deer are important in maintaining the disease because the ticks feed and mate on them. They are a dead-end host and do not become infected. Although their blood may contain a few of the pathogens, they are much less likely than mice to carry nymphs or to infect the nymphs.

The tick (one of two *Ixodes* species) feeds three times during its life cycle (**Figure 23.13a**). The first and second feedings, as a larva and then as a nymph, are usually on a field mouse. The

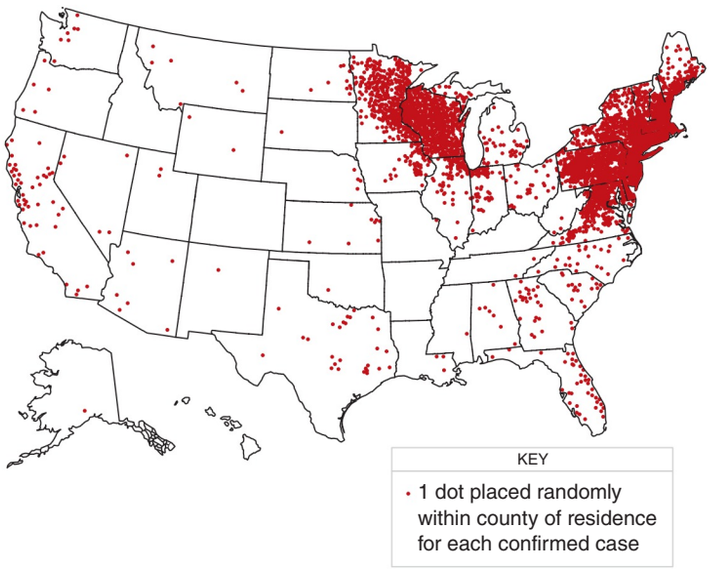


Figure 23.12 Lyme disease in the United States, reported cases by county, 2012

Source: CDC.

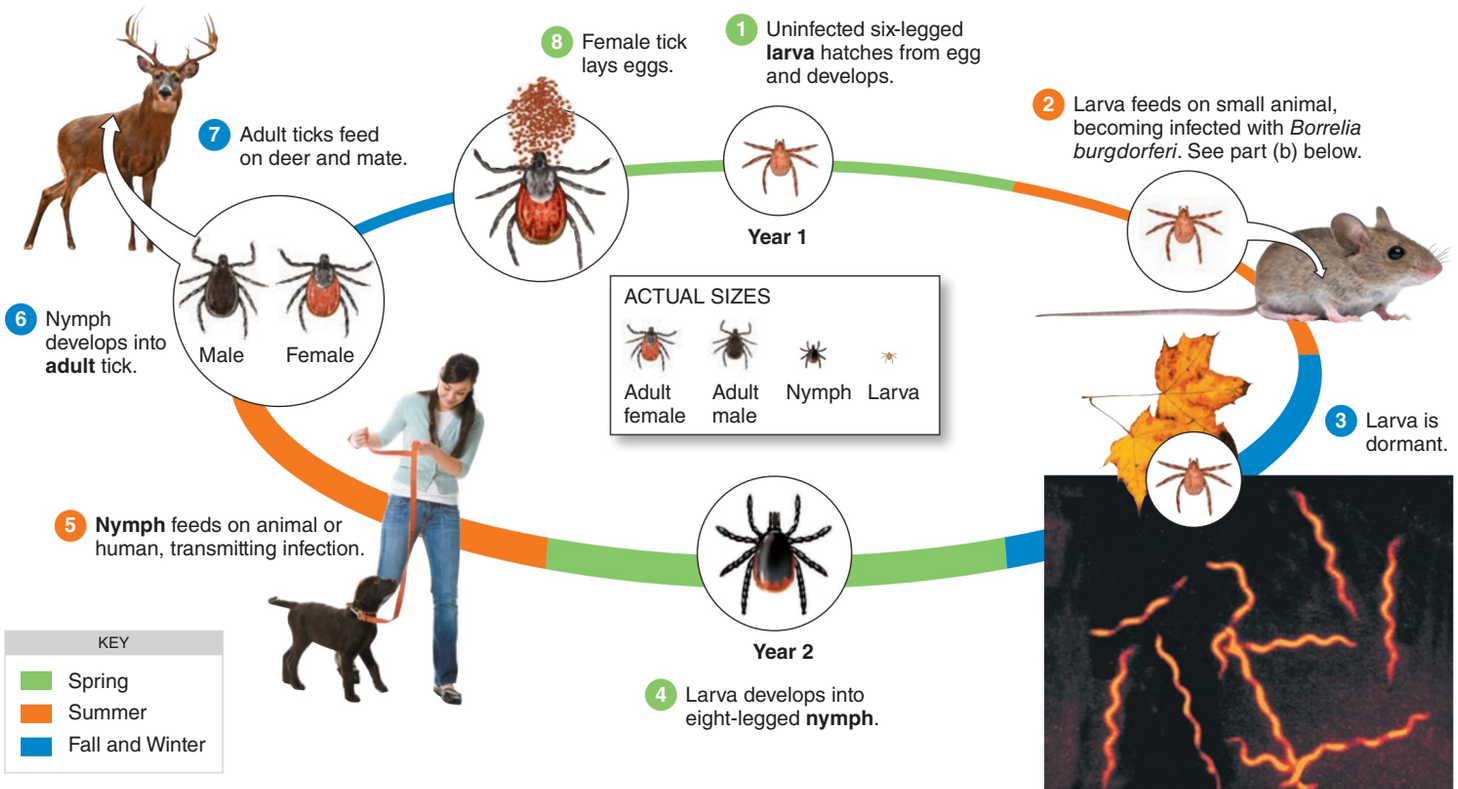
Q What factors are responsible for the geographic distribution of Lyme disease?

third feeding, as an adult, is usually on a deer. These feedings are separated by several months, and the ability of the spirochete to remain viable in the disease-tolerant field mice is crucial to maintaining the disease in the wild.

On humans, the ticks usually attach from a perch on shrubs or grass. They do not feed for about 24 hours, and it usually requires 2 or 3 days of attachment before transfer of bacteria and infection occur. Probably only about 1% of tick bites result in Lyme disease.

On the Pacific coast, the tick that transmits Lyme disease is the western black-legged tick *Ixodes pacificus* (IKS-ō-des pah-SI-fi-kus) (see also Figure 12.31b, page 351). In the rest of the country, *Ixodes scapularis* (skap-ū-LAR-is) is most often responsible. This latter tick is so small that it is often missed. On the Atlantic coast, almost all *Ixodes* ticks carry the spirochete (Figure 23.13b); on the Pacific coast, few are infected because that tick feeds on lizards that do not carry the spirochete effectively.

The first symptom of Lyme disease is usually a rash that appears at the bite site. It is a red area that clears in the center as it expands to a final diameter of about 15 cm (**Figure 23.14**). This



(a) The tick, *Ixodes scapularis*, has a 2-year life cycle in which it requires three blood meals. The tick is infected by its first blood meal and can pass on the infection to a human in its second.

(b) The cause of Lyme disease, *Borrelia burgdorferi*

Figure 23.13 The life cycle of the tick vector of Lyme disease.

Q What other diseases are transmitted by ticks?

distinctive rash occurs in about 75% of cases. Flulike symptoms appear in a couple of weeks as the rash fades. Antibiotics taken during this interval are very effective in limiting the disease.

During a second phase, in the absence of effective treatment, there is often evidence that the heart is affected. The heartbeat may become so irregular that a pacemaker is required. Incapacitating, chronic neurological symptoms, such as facial paralysis, oppressive fatigue, and memory loss may be present. Some cases result in meningitis and encephalitis. In a third phase, months or years later, some patients develop arthritis that may affect them for years. Immune responses to the presence of the bacteria are probably the cause of this joint damage. No vaccine for human use is available; one marketed in 1998 was later withdrawn. (However, a vaccine is available for veterinary use in dogs.) Natural immunity to reinfection appears to be variable. For example, patients who have progressed to the stage of Lyme arthritis appear to have considerable immunity against reinfection, whereas patients at the earlier stages of the disease do not.

Diagnosis of Lyme disease depends partly on the symptoms and an index of suspicion based on the prevalence in the geographic area. Physicians are cautioned that serological tests must be interpreted in conjunction with clinical symptoms and the likelihood of exposure to infection. Serological tests are challenging to interpret, and following a positive initial ELISA (page 509) or indirect fluorescent-antibody (FA) test (page 507), confirmation should be attempted with a Western blot test (page 278). Also, after effective antibiotic treatment eliminates the bacteria, antibodies—even IgM antibodies—often persist for years and may confuse later attempts at diagnosis.

Several antibiotics are effective in treating the disease, although in the later stages, large amounts and very extended administration times may be needed.

Ehrlichiosis and Anaplasmosis

Human monocytotropic ehrlichiosis (HME) is caused by *Ehrlichia chafeensis* (er-LIK-ē-ah chaf-FĒ-en-sis). This is a gram-negative, rickettsia-like, obligately intracellular bacterium. Aggregates of bacteria—called *morulae,* the Latin word for mulberry—form within the cytoplasm of monocytes. *E. chafeensis* was first observed in a human case in 1986; previously it had been considered a solely veterinary pathogen. HME is a tickborne disease; the common name for the usual vector is the Lone Star tick. Cases occasionally occur where this tick is not found, so there may be other vectors. The white-tailed deer is the main animal reservoir, but it does not show signs of illness.

A similar tickborne disease, **human granulocytic anaplasmosis (HGA),** was formerly called *human granulocytic ehrlichiosis.* The change occurred when the causative organism, an obligate intracellular bacterium formerly grouped with the ehrlichia, was renamed A*naplasma phagocytophilum* (an-ah-PLAZ-mah fag′ō-si-TAH-fi-lum). The tick vector is *Ixodes scapularis,* the same genus of vector as Lyme disease and babesiosis (page 340).



Figure 23.14 The common bull's-eye rash of Lyme disease. The rash is not always this obvious.

Q What symptoms occur once the rash fades?

The symptoms of these diseases are identical, and HGA was identified only when a case occurred in Wisconsin, where the Lone Star tick was unknown. Patients suffer from a flulike disease with high fever and headache; the fatality rate is less than 5%. The diseases probably occur with a frequency much higher than reported. Cases of HME and HGA are both widespread and sometimes geographically overlap. Once either disease is suspected (often from detection of morulae in blood smears), diagnosis is usually by the indirect FA test for HME and a polymerase chain reaction (PCR) test (page 243) for HGA. Therapy with antibiotics such as doxycycline is usually effective.

Typhus

The various typhus diseases are caused by rickettsias, bacteria that are obligate intracellular parasites of eukaryotes. Rickettsias, which are spread by arthropod vectors, infect mostly the endothelial cells of the vascular system and multiply within them. The resulting inflammation causes local blockage and rupture of the small blood vessels.

Typhus Fever (Epidemic Louseborne Typhus) Typhus fever is caused by *Rickettsia prowazekii* and is carried by the human body louse *Pediculus humanus corporis* (pe-DIK-u-lus hu-MAN-us KOR-por-is) (see Figure 12.32a, page 352). The pathogen grows in the gastrointestinal tract of the louse and is excreted by it. It is transmitted when the feces of the louse are rubbed into the wound when the bitten host scratches the bite. The disease flourishes in crowded and unsanitary surroundings, when lice can transfer readily from an infected host to a new host. Although a rare disease in the United States, several cases have occurred in the eastern states from contact with flying squirrels or their nests. Anne Frank, the teenaged writer of the famed

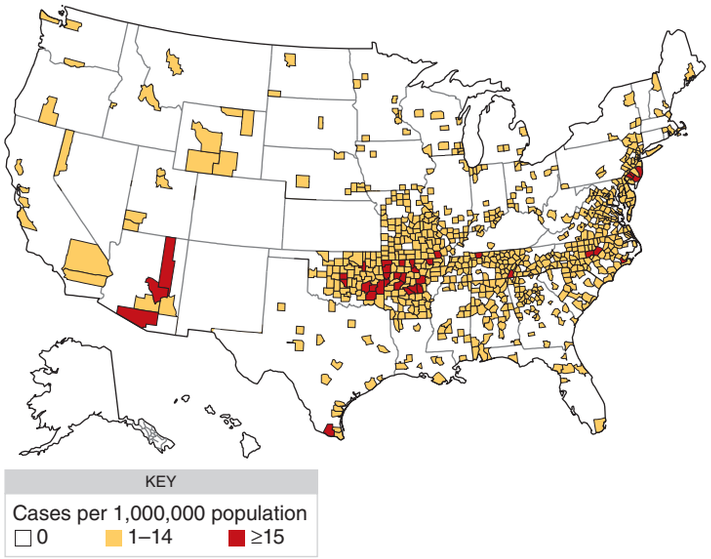


Figure 23.15 The U.S. geographic distribution of Rocky Mountain spotted fever (tickborne typhus), 2011.

Source: CDC, *MMWR* 60(53), July 5, 2013.

Q Geographically, is this a disease of rural or urban areas?

World War II diary, died of typhus contracted in concentration camp conditions.

Typhus fever produces a high and prolonged fever that lasts at least 2 weeks. Stupor and a rash of small red spots caused by subcutaneous hemorrhaging are characteristic, as the rickettsias invade blood vessel linings. Mortality rates are very high when the disease is untreated.

Tetracycline and chloramphenicol are usually effective against typhus fever, but eliminating conditions in which the disease flourishes is more important. The microbe is considered especially hazardous, and attempts to culture it require extreme care. Vaccines are available for military populations, which historically have been highly susceptible to the disease.

Endemic Murine Typhus Transmitted by the rat flea *Xenopsylla cheopis* (see Figure 12.32b, page 352) **endemic murine typhus** occurs sporadically rather than in epidemics. The term *murine* (derived from Latin for mouse) refers to the fact that rodents, such as rats and squirrels, are the common hosts for this type of typhus. The pathogen responsible for the disease is *Rickettsia typhi,* a common inhabitant of rats. With a mortality rate of less than 5%, the disease is considerably less severe than typhus fever. Except for the reduced severity of the disease, endemic murine typhus is clinically indistinguishable from typhus fever. Tetracycline and chloramphenicol are effective treatments for endemic murine typhus, and rat control is the best preventive measure.

Spotted Fevers Tickborne typhus, or **Rocky Mountain spotted fever,** is probably the best-known rickettsial disease in the United States. It is caused by *Rickettsia rickettsii.* Despite its name (it was first recognized in the Rocky Mountain area), it is most common in the southeastern states and Appalachia (Figure 23.15). This rickettsia is a parasite of ticks and is usually passed from one generation of ticks to another through their eggs, a mechanism called *transovarian passage* (Figure 23.16). Surveys show that in endemic areas, perhaps 1 out of every 1000 ticks is infected. In different parts of the United States, different ticks are involved—in the west, the wood tick *Dermacentor andersoni* (der-mah-SEN-ter AN-der-son-ē); in the east, the dog tick *Dermacentor variabilis* (VAR-ē-ah-bi-lis).

About a week after the tick bites, a macular rash develops that is sometimes mistaken for measles (Figure 23.17); however, it often appears on palms and soles, where viral rashes do not occur. The

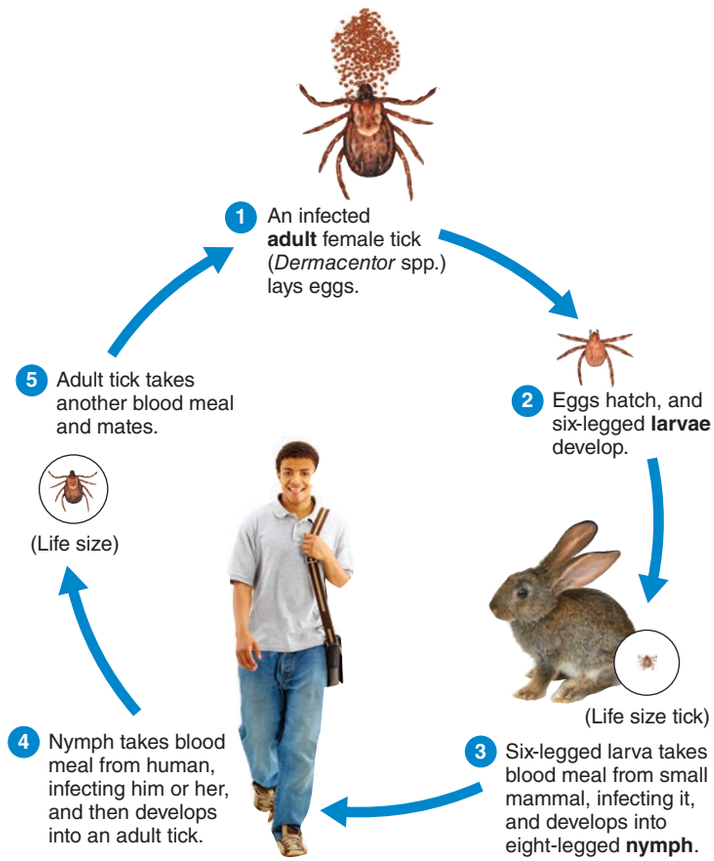


Figure 23.16 The life cycle of the tick vector (*Dermacentor* spp.) of Rocky Mountain spotted fever. Mammals are not essential to survival of the pathogen, *Rickettsia rickettsii,* in the tick population; the bacteria may be passed by transovarian passage, so new ticks are infected upon hatching. A blood meal is required for ticks to advance to the next stage in the life cycle.

Q What is meant by *transovarian passage*?



Figure 23.17 The rash caused by Rocky Mountain spotted fever. This rash is often mistaken for measles. People with dark skin have a higher mortality rate because the rash is often not recognized early enough for effective treatment.

Q How can Rocky Mountain spotted fever be prevented?

rash is accompanied by fever and headache. Death, which occurs in about 3% of the approximately 2000 cases reported each year, is usually caused by kidney and heart failure.

Serological tests don't become positive until late in the illness. Diagnosis before the typical rash appears is difficult because symptoms vary widely. Also, on dark-skinned individuals, the rash is difficult to see. A misdiagnosis can be costly; if treatment is not prompt and correct, the mortality rate is about 20%.

Antibiotics such as tetracycline and chloramphenicol are very effective if administered early enough. No vaccine is available.

Clinical Case

Katie is referred to a local emergency department (ED) for further evaluation and management. At the ED, Katie has a normal temperature of 37.1°C. A complete blood cell (CBC) count reveals a white blood cell count of 3900/µl and a platelet count of 115,000/µl. Her evaluation includes a computed tomography (CT) scan of her head and lumbar puncture. The CT scan does not reveal any brain trauma or injury, and her cerebrospinal fluid (CSF) does not show the presence of bacteria. Katie's light-headedness resolves later that evening, and she is sent home after spending half the day in the ED.

What do her CBC results indicate? (Hint: Refer to Chapter 16.)

CHECK YOUR UNDERSTANDING

- Why is the plague-infected flea so eager to feed on a mammal? **23-10**
- What animal does the infecting tick feed on just before it transmits Lyme disease to a human? **23-11**
- Which disease is tickborne: epidemic typhus, endemic murine typhus, or Rocky Mountain spotted fever? **23-12**

Viral Diseases of the Cardiovascular and Lymphatic Systems

LEARNING OBJECTIVES

23-13 Describe the epidemiologies of Burkitt's lymphoma, infectious mononucleosis, and CMV inclusion disease.

23-14 Compare and contrast the causative agents, vectors, reservoirs, and symptoms of yellow fever, dengue, dengue hemorrhagic fever, and chikungunya fever.

23-15 Compare and contrast the causative agents, reservoirs, and symptoms of Ebola hemorrhagic fever and *Hantavirus* pulmonary syndrome.

Viruses cause a number of cardiovascular and lymphatic diseases, prevalent mostly in tropical areas. However, one viral disease of this type, infectious mononucleosis, is an especially familiar infectious disease among American college-aged individuals.

Burkitt's Lymphoma

In the 1950s, Denis Burkitt, an Irish physician working in eastern Africa, noticed the frequent occurrence in children of a fast-growing tumor of the jaw (**Figure 23.18**). Known as **Burkitt's lymphoma,** this is the most common childhood cancer in Africa. It has a limited geographic distribution similar to that of malaria in central Africa.

Burkitt suspected a viral cause of the tumor and a mosquito vector. At that time, there was no known virus that caused human cancer, although several viruses were clearly associated with animal cancers. Intrigued by this possibility, in 1964 British virologist Tony Epstein and his student, Yvonne Barr, performed biopsies on the tumors. A virus was cultured from this material, and the electron microscope showed a herpeslike virus in the culture cells; it was named the *Epstein-Barr virus (EB virus).* The official name of this virus is *human herpesvirus 4.*

EB virus is clearly associated with Burkitt's lymphoma, but the mechanism by which it causes the tumor isn't understood. Research eventually showed, however, that mosquitoes don't transmit the virus or the disease. Instead, mosquito-borne malarial infections apparently foster the development of Burkitt's lymphoma by impairing the immune response to EB virus, which is almost universally present in human adults worldwide. The virus has, in fact, become so adapted to humans that it is one of our most effective parasites. It establishes a

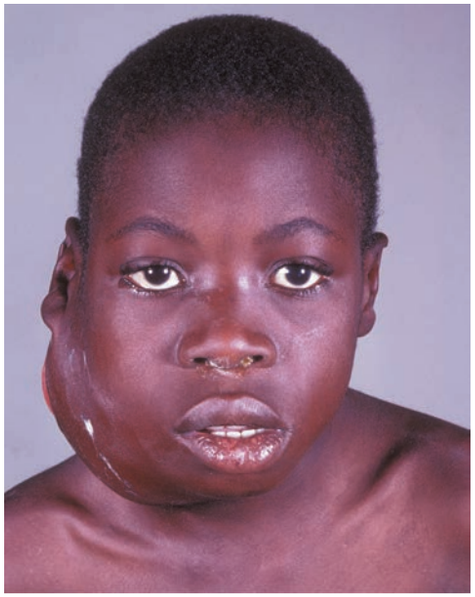


Figure 23.18 A child with Burkitt's lymphoma. Cancerous tumors of the jaw caused by Epstein-Barr virus (EB virus) are seen mainly in children. This child was successfully treated.

Q What is the relationship between malarial areas and areas with Burkitt's lymphoma?

lifelong infection in most people (**Figure 23.19**) that is harmless and rarely causes disease.

In areas without endemic malaria, such as the United States, Burkitt's lymphoma is rare and is usually abdominal. The appearance of the lymphoma in AIDS patients is an indication of the importance of immune surveillance in preventing expression of the disease.

CHECK YOUR UNDERSTANDING

Although not a disease with an insect vector, why is Burkitt's lymphoma most commonly a disease found in malarial areas? **23-13**

Infectious Mononucleosis

The identification of EB virus as the cause of **infectious mononucleosis,** or *mono,* resulted from one of the accidental discoveries that often advance science. A technician in a laboratory investigating EB virus served as a negative control for the virus. While on vacation, she contracted an infection characterized by fever, sore throat, swollen lymph nodes in the neck, and general weakness. The most interesting aspect of the technician's disease was that she now tested serologically positive for EB virus. It was soon confirmed that the same virus that is associated with Burkitt's lymphoma also causes almost all cases of infectious mononucleosis.

In developing parts of the world, infection with EB virus occurs in early childhood, and over 95% of adults have acquired antibodies. Nearly 20% of adults in the United States carry EB virus in oral secretions. Childhood EB virus infections are usually asymptomatic, but if infection is delayed until young adulthood, as is often the case in the United States, the result is more symptomatic probably because of an intense immunological response. The peak U.S. incidence of the disease occurs at about age 15 to 25. A principal cause of the rare deaths is rupture of the enlarged spleen (a common response to a systemic infection) during vigorous activity. Recovery is usually complete in a few weeks, and immunity is permanent.

The usual route of infection is by the transfer of saliva by kissing or, for example, by sharing drinking vessels. It doesn't spread among casual household contacts, so aerosol transmission is unlikely. The incubation period before appearance of symptoms is 4 to 7 weeks.

EB virus maintains a persistent infection in the mouth and throat, which accounts for its presence in saliva. It is probable that resting memory B cells (see Figure 17.6, page 476) located in lymphoid tissue are the primary site of replication and persistence. Most of the symptoms are attributed to responses of T cells to the infection.

The disease name *mononucleosis* refers to lymphocytes with unusual lobed nuclei that proliferate in the blood during the acute infection (**Figure 23.20**). The infected B cells produce heterophile antibodies, so called from the Greek *hetero* (different) and *phile* (affinity). These are weak antibodies with multispecific activities; their significance is that they are used in the diagnosis of mono. If this test is negative, the symptoms may be caused by cytomegalovirus (see page 657) or several other disease conditions. A fluorescent-antibody test that detects IgM antibodies against EB virus is the most specific diagnostic method. There is no recommended therapy for most patients.

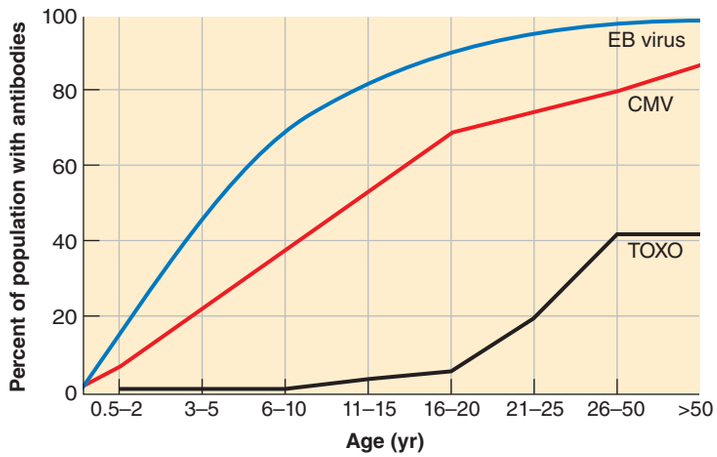


Figure 23.19 The typical U.S. prevalence of antibodies against Epstein-Barr virus (EB virus), cytomegalovirus (CMV), and *Toxoplasma gondii* (TOXO) by age.

Source: Laboratory Management, June 1987, pp. 23ff.

Q To judge from this graph, which of these diseases is more likely to result from early-childhood infections?

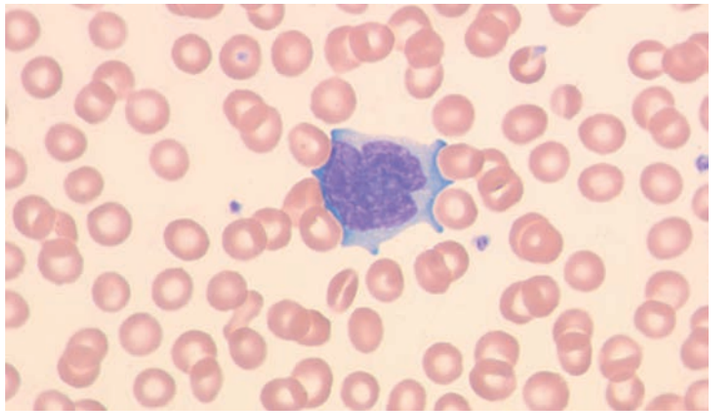


Figure 23.20 A lymphocyte with the unusual lobed nucleus that is characteristic of mononucleosis.

Q What antibodies indicate a patient has mono?

Other Diseases and Epstein-Barr Virus

We have just discussed two diseases, Burkitt's lymphoma and infectious mononucleosis, for which there is a clear association with EB virus. There is a lengthy list of diseases for which there is a suspected, but not proven, relationship with EB virus. Some of the more familiar of these include **multiple sclerosis** (autoimmune attack on the nervous system), **Hodgkin's lymphoma** (tumors of the spleen, lymph nodes, or liver), and **nasopharyngeal** (nose and pharynx) **cancer** among certain ethnic groups in southeast Asia and Inuits.

Cytomegalovirus Infections

Almost all of us will become infected with *cytomegalovirus (CMV)* during our lifetime. The CMV is a very large herpesvirus that, much like the Epstein-Barr virus, probably remains latent in white blood cells, such as monocytes, neutrophils, and T cells. It is not much affected by the immune system, replicating very slowly and escaping antibody action by moving between cells that are in contact. Carriers of the virus may shed it in body secretions such as saliva, semen, and breast milk. When CMV infects a cell, it causes the formation of distinctive inclusion bodies that are visible by microscopy. When these bodies occur in pairs, they are known as "owl's eyes" and are useful in diagnosis. These inclusion bodies were first reported in 1905 in certain cells of newborn infants affected with congenital abnormalities. The cells were also enlarged, a condition known as *cytomegaly,* from which the virus eventually received its name. This disease of the newborns was given the name of *cytomegalic inclusion disease (CID).* The inclusion bodies were originally thought to be stages in the life cycle of a protozoan, and a viral cause of the disease was not proposed until 1925. The cytomegalovirus wasn't isolated until some 30 years after that. The official name is *human herpesvirus 5.*

In the United States, about 8000 infants each year are born suffering symptomatic damage from CID, the most serious of which includes severe mental retardation or hearing loss. If the mother is already infected before conception, the rate of transmission to a fetus is less than 2%, but if the primary infection occurs during pregnancy, the rate of transmission is in the range of 40–50%. Tests to determine the immune status of the mother are available, and it's recommended that physicians determine the immune status of female patients of childbearing age. All non-immune women should be informed of the risks of infection during pregnancy. A complicating factor is that women who are CMV positive before conception might still be infected with new strains of CMV and transmit it to the fetus.

In healthy adults, acquiring a CMV infection causes either no symptoms or those resembling a mild case of infectious mononucleosis. It has been said that if CMV were accompanied by a skin rash, it would be one of the better-known childhood diseases. It is therefore not surprising, given that 80% of the population of the United States is estimated to carry the virus, that CMV is a common opportunistic pathogen in persons whose immune systems have become compromised. Figure 23.19 shows the prevalence of antibodies against CMV, Epstein-Barr virus, and *Toxoplasma gondii* (page 663). In developing parts of the world, infection rates of CMV approach 100%. For immunocompromised individuals, CMV is a frequent cause of a life-threatening pneumonia, but almost any organ can be affected. About 85% of AIDS patients exhibit a CMV-caused eye infection, *cytomegalovirus retinitis.* Without treatment, it results in eventual loss of vision. To prevent transmission of CMV during transplantation procedures, an immunoglobulin preparation containing a standardized amount of antibody is recommended. For treatment of CMV illness, ganciclovir has been the mainstay. A suitable alternative, if resistance to this antibiotic develops, is foscarnet.

CMV is transmitted mostly by activities that result in contact with body fluids that contain the virus, such as kissing, and it is very common among children in day-care settings. It can also be transmitted sexually, by transfused blood, and by transplanted tissue. Transmission by transfused blood can be eliminated by filtering out the white cells from the blood or by serological testing of the donor for the virus. Transplanted tissue is usually tested for the virus, and products are now available that contain antibodies to neutralize CMV present in donated tissue. Vaccines are under development, but none is currently available.

Chikungunya Fever

The recent introduction of the West Nile virus into the United States has shown that a tropical mosquito-borne disease can spread in temperate climates. Rapid travel and climatic warming, among other factors, are making similar vector-borne diseases a global phenomenon. Another tropical disease now causing concern is **chikungunya fever** (the name sounds like "chicken-gun-yah," but the disease is often referred to simply as *chik*).

BIG PICTURE

Climate Change and Disease

A disease normally found only in Africa and Asia spreads to the Americas, and public health officials warn that climate change may bring a rising tide of vector-borne diseases to the United States.

Chikungunya fever is a viral disease with symptoms similar to dengue. Until recently, cases outside Africa and Asia were found only among people who had traveled to endemic regions. However, in 2013 the first indigenous cases appeared in the Western Hemisphere. By February 2013, officials reported 3700 confirmed cases in the Caribbean, including outbreaks in the British Virgin Islands, Dominica, French Guiana, Guadalupe, and Saint Barthelemy. In the U.S., there have been 580 imported cases and four acquired in the U.S. was reported in Florida.

The Challenge of Controlling Mosquitoes That Spread Chikungunya Fever

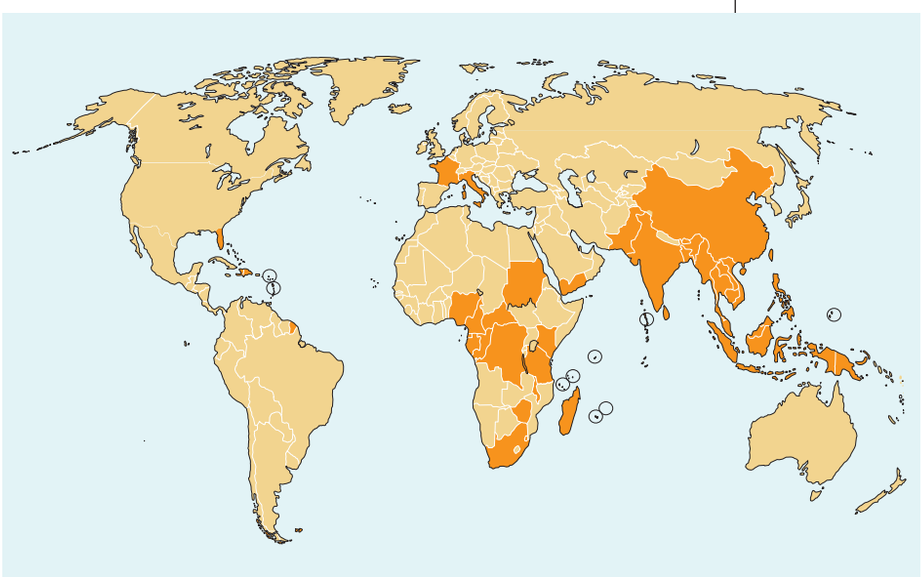
There is no vaccine, so the best way to prevent chikungunya's spread is vector control. The vectors are *Aedes aegypti,* known as the yellow fever mosquito, and *A. albopictus,* known as the Asian tiger mosquito. Yellow fever mosquitoes tend to live in tropical or subtropical regions and are also the main vector of dengue. The Asian tiger mosquito can also transmit dengue and West Nile virus. It is an invasive species introduced to the Americas through sea cargo containers.

Unlike many other mosquitoes, both species that transmit chikungunya feed all day long rather than just at dusk. The Asian tiger mosquito prefers feeding on humans over other animals and frequently lives inside buildings or very near them.

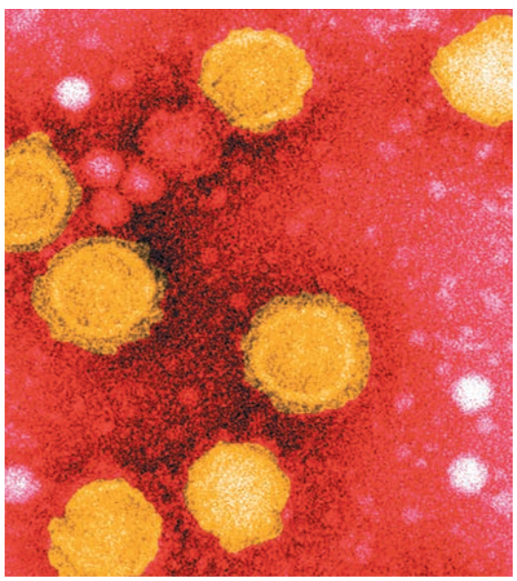
The Asian tiger mosquito has been moving north and east since its introduction in 1987. At present, the northernmost boundary is New Jersey and southern New York. If temperatures and rainfall rise as predicted over the next century, then the range of the Asian tiger mosquito will also grow. One study suggests about 50% of the land in the northeastern United States, where about 30 million people reside, could become habitat for the Asian tiger mosquito by the year 2080. This will likely facilitate the spread of chikungunya and other diseases now considered tropical throughout most of the U.S. East Coast as well.



Asian tiger mosquito, *A. albopictus,* a chikungunya vector



Countries and territories where chikungunya cases have been reported (as of August, 2014). *Source:* CDC.



TEM of chikungunya virus

Searching for New Methods of Vector Control

Traditional mosquito control efforts focus on eliminating standing water sources used by mosquitoes to breed, along with spraying larvicides or insecticides in mosquito-prone areas. But total elimination of standing water is nearly impossible, and effective reduction requires full community support. Additionally, insecticides don't work as well for the indoor-dwelling Asian tiger mosquitoes as they do for species that live outside. Bed nets can provide some protection within a home, but because Asian mosquitoes feed all day long, this method isn't very effective in controlling this species.

Some Methods of Control

- **Water Storage Covers** are inexpensive wooden covers on concrete water storage containers. Their use in one community in India ended the main breeding location for Asian tiger mosquitoes.
- **Ovitraps** are cylindrical containers are designed to be attractive egg-laying sites. They contain mesh that prevents mature mosquitoes escaping from the containers later. Some ovitraps also have paddles coated with sticky material that trap the egg-laying females.
- **Biological Controls** include release of larvae-eating copepods (a crustacean), mosquito fish, dragonflies, and beetle larvae in breeding areas. "Mosquito dunks," some of which contain *Bacillus thuringiensis israelensis* bacteria, are slow-dissolving blocks that can be added to ponds or fountains to kill larvae. There have also been some sites where genetically modified sterile male mosquitoes were released to cut down population growth.

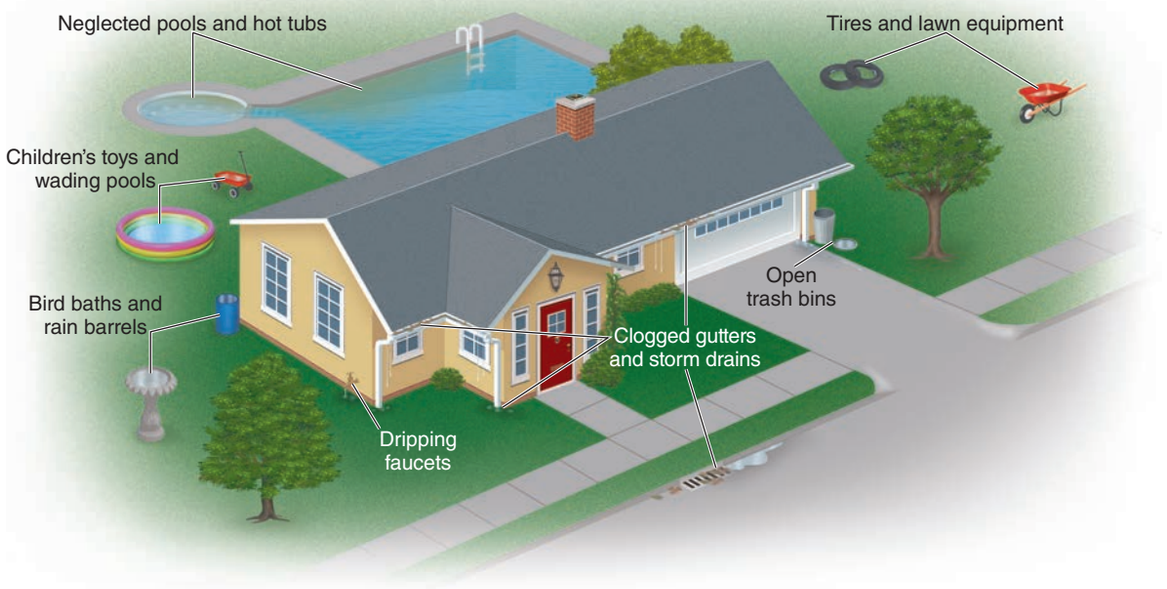


Biological controls include "mosquito dunks" like the one shown above that are placed in ponds or fountains and kill larvae.

KEY CONCEPTS

- When climate changes, certain insects that vector diseases may spread into new areas, causing new outbreaks as they go. **(See Chapter 12, "Arthropods as Vectors," pages 351–353, and Chapter 14, "Transmission of Disease," pages 399–402.)**
- *Bacillus thuringiensis* is used in mosquito dunks, one method of mosquito control. **(See Chapter 11, "Bacillales," pages 309–310.)**

Common mosquito habitats around your home



Eliminating sources of standing water is a main line of attack in controlling mosquito populations. The illustration above shows common sources of standing water in homes.

The name comes from an African language and means "that which bends up." The symptoms are a high fever and severe, crippling joint pains—especially in the wrists, fingers, and ankles—that can persist for weeks or months. There is often a rash and even massive blisters. The death rate is very low. The vector is the *Aedes* mosquito, primarily *Aedes aegypti* (Ā-e-dēz ē-JIP-tē), which spreads the disease widely in Asia and Africa. Recent outbreaks have also been caused by *A. albopictus* (al-BŌ-pik-tus). A mutation in the virus, which is related to the virus causing western equine encephalitis (WEE) and eastern equine encephalitis (EEE) (page 624), has adapted the virus to multiply in this insect. It is uncertain whether there is an animal reservoir. More than half a million cases have occurred throughout the Caribbean since the first case was reported in the Western Hemisphere in 2013. An outbreak has already occurred in Italy, and locally acquired cases have occurred in Florida.

A. albopictus is also known as the Asian tiger mosquito because of its bright white stripes. Well adapted to urban settlements, it also survives cold climates and will probably become established eventually even in the northern parts of the United States and the coastal areas of Scandinavia. Because it is an extremely aggressive daytime biter, it is a serious nuisance for outdoor activities. Of greater concern to health officials is that *A. albopictus* is known, so far, to transmit both chikungungya fever and dengue, a disease that will be discussed shortly.

Classic Viral Hemorrhagic Fevers

Yellow Fever

Most hemorrhagic fevers are zoonotic diseases; they appear in humans only from infectious contact with their normal animal hosts. Some of them have been medically familiar for so long that they are considered "classic" hemorrhagic fevers. First among these is **yellow fever.** The yellow fever virus is injected into the skin by a mosquito, *A. aegypti.*

In the early stages of severe cases of the disease, the person experiences fever, chills, and headache, followed by nausea and vomiting. This stage is followed by jaundice, a yellowing of the skin that gave the disease its name. This coloration reflects liver damage, which results in the deposit of bile pigments in the skin and mucous membranes. The mortality rate for yellow fever is high, about 20%.

Yellow fever is still endemic in many tropical areas, such as Central America, tropical South America, and Central Africa. At one time, the disease was endemic in the United States and occurred as far north as Philadelphia. The last U.S. case of yellow fever occurred in Louisiana in 1905 during an outbreak that resulted in about 1000 deaths. Mosquito eradication campaigns initiated by the U.S. Army surgeon Walter Reed were effective in eliminating yellow fever in the United States.

Monkeys are a natural reservoir for the virus, but human-to-human transmission can maintain the disease. Local control of mosquitoes and immunization of the exposed population are effective controls in urban areas.

Diagnosis is usually by clinical signs, but it can be confirmed by a rise in antibody titer or isolation of the virus from the blood. There is no specific treatment for yellow fever. The vaccine is an attenuated live viral strain and yields a very effective immunity.

Dengue and Severe Dengue

Compared to yellow fever, dengue (DEN-gē) is a similar but milder disease also transmitted by *A. aegypti* mosquitoes. This disease is endemic in the Caribbean and other tropical environments. Globally, an estimated 50 million cases in at least 100 countries occur annually. The countries surrounding the Caribbean are reporting an increasing number of cases of dengue. In most years, more than 100 cases are imported into the United States, mostly by travelers from the Caribbean and South America.

Most infections by the virus causing dengue are asymptomatic, and the disease itself may vary from a mild case of fever to a severe, fatal disease. At one time patients with dengue were classified as suffering from either dengue fever or dengue hemorrhagic fever. Recently the WHO has changed the system of classification. Patients who recover without major incident are classified as having **dengue.** If the patient suffers from severe bleeding and organ impairment, the case is classified as **severe dengue.**

The disease is a leading cause of death among southeast Asian children. It does not appear to have an animal reservoir. The primary mosquito vector for dengue is common in the Gulf states. Several cases of dengue acquired in Florida since 2010 have raised concern about the potential for emergence of dengue in the U.S. An efficient secondary vector, *Aedes albopictus,* has also expanded widely in range in recent years. Attempts to control dengue by

Clinical Case

Katie's lowered white blood cell count (leukopenia) may indicate a viral infection. Four days later, Katie returns to her primary care provider: her gums are bleeding, and she "just doesn't feel right." On examination, Katie has a temperature of 37.1°C, but now she has a rash on her legs. When asked, Katie explains that the rash is from scratching the numerous mosquito bites she incurred while in Key West. Katie's doctor doesn't think the rash looks like it's from mosquito bites; he sends a serum sample to a private lab for testing. IgM antibodies for dengue are reported in her serum. After Katie's physician notifies the public health department of the test result, Katie's earlier serum specimen, CSF specimen, and a repeat serum specimen are sent to CDC for confirmatory testing.

What does the presence of IgM antibodies mean?

638 655 660 664 670

vector control have not met with success. It has proven difficult to develop a safe and effective vaccine, and none is currently available. Similarly, effective antiviral drugs have yet to be developed.

CHECK YOUR UNDERSTANDING

Why is the mosquito *Aedes albopictus* a special concern to the populations of temperate climates? **23-14**

Emerging Viral Hemorrhagic Fevers

Certain other hemorrhagic diseases are considered new or "emerging" hemorrhagic fevers. In 1967, 31 people became ill and 7 died after contact with some African monkeys that were imported into Europe. The virus was strangely shaped (in the form of a filament [filoviruses]) and was named for the site of the laboratory outbreak in Germany, the **Marburg virus,** or **green monkey virus.** The symptoms of infection by hemorrhagic viruses are mild at first; headache and muscle pain. But after a few days the victim suffers from high fever and begins vomiting blood and bleeding profusely, both internally and from external openings such as the nose and eyes. Death comes in a few days from organ failure and shock.

A similar hemorrhagic fever, **Lassa fever,** appeared in west Africa in 1969 and was traced to a rodent reservoir. The *Lassa virus,* an arenavirus, is present in the rodent's urine and is the source of human infections. Outbreaks of Lassa fever have killed thousands.

Seven years later, outbreaks in Africa of another highly lethal hemorrhagic fever were caused by *Ebolavirus,* a filovirus similar to the Marburg virus (Figure 23.21). The walls of the blood vessels are damaged, the virus interferes with coagulation, and blood leaks into surrounding tissue. Named **Ebola hemorrhagic fever** (EHF), for a regional river, this is now a well-publicized disease, with mortality approaching 90%. The natural host reservoir for the Ebola virus is probably a cave-dwelling fruit bat, which is used as food and is not acutely affected by the virus it carries. Once a human is infected and shedding blood, the infection is spread by contact with the blood and body fluids and in many cases by the reuse of needles used on patients. The local custom of washing the body before burial often triggers new infections. The occurrence of EHF in the United States in 2014 demonstrates how modern air travel contributes to disease emergence.

South America has several hemorrhagic fevers caused by Lassa-like viruses (arenaviruses) that are maintained in the rodent population. **Argentine** and **Bolivian hemorrhagic fevers** are transmitted in rural areas by contact with rodent excretions. A recent handful of deaths in California have been attributed to the **Whitewater Arroyo virus,** an arenavirus with a reservoir in wood rats. These are the first reports of arenavirus-caused hemorrhagic disease in the Northern Hemisphere.

***Hantavirus* pulmonary syndrome,** caused by the *Sin Nombre virus,** a bunyavirus, has become well known in the United States because of several outbreaks, mostly in the western states. It manifests itself as a frequently fatal pulmonary infection, in which the lungs fill with fluids. The main treatment is mechanical respiration; the antiviral ribavirin is recommended, but its value is uncertain. Actually, *Hantavirus*-caused diseases have a long history, especially in Asia and Europe. It is best known there as **hemorrhagic fever with renal syndrome** and primarily affects renal (kidney) function. All these related diseases are transmitted by the inhalation of viruses in dried urine and feces from infected small rodents. Worldwide, there are at least 14 known disease-causing hantaviruses.

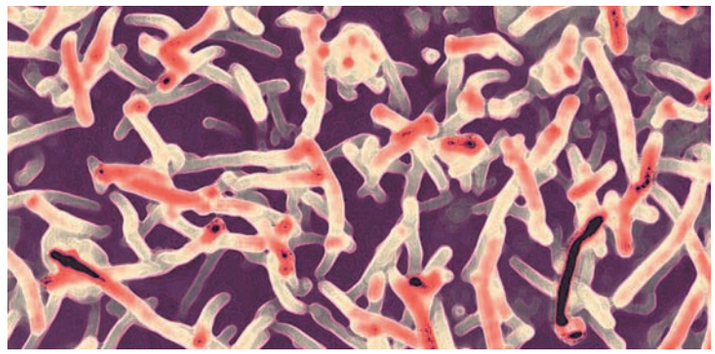


Figure 23.21 Ebola hemorrhagic virus. The viruses causing Ebola hemorrhagic fever are shown here. They disrupt the blood clotting system.

Can you see why the Ebola virus is called a filovirus?

Diseases in Focus 23.4 describes the various viral hemorrhagic fevers.

CHECK YOUR UNDERSTANDING

Which disease does Ebola hemorrhagic fever more closely resemble, Lassa fever or *Hantavirus* pulmonary syndrome? **23-15**

Protozoan Diseases of the Cardiovascular and Lymphatic Systems

LEARNING OBJECTIVES

23-16 Compare and contrast the causative agents, modes of transmission, reservoirs, symptoms, and treatments for Chagas' disease, toxoplasmosis, malaria, leishmaniasis, and babesiosis.

23-17 Discuss the worldwide effects of these diseases on human health.

Protozoa that cause diseases of the cardiovascular and lymphatic systems often have complex life cycles, and their presence may affect human hosts seriously.

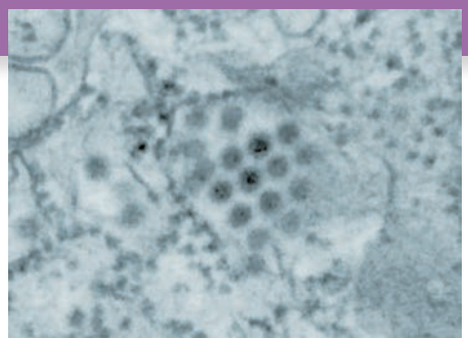
*The virus causing the pulmonary *Hantavirus* outbreak in 1993 in the Four Corners area of the southwestern United States (Arizona, Utah, Colorado, and New Mexico) was originally called the Four Corners virus. Local authorities were concerned about the effect of this name on tourism in the area and complained. The name Sin Nombre, Spanish for no name, was then adopted.

DISEASES IN FOCUS 23.4

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers are endemic in tropical countries where, except for dengue, they are found in small mammals. However, increasing international travel has resulted in importation of these viruses into the United States. There is no treatment.

The CDC's Special Pathogens Branch has specialized containment facilities to confirm diagnosis of viral hemorrhagic fevers by serology, nucleic acids, and virus culture. Use the table below to make a differential diagnosis and identify the cause of a rash and severe joint pain in a 20-year-old woman. For the solution, go to MasteringMicrobiology.



Small viruses seen by electron microscopy in a patient's tissues. Upon isolation, they were identified as single-stranded RNA viruses in the family Flaviviridae.

Disease	Pathogen	Portal of Entry	Symptoms	Reservoir	Method of Transmission	Prevention
Yellow Fever	Flavivirus (yellow fever virus)	Skin	Fever, chills, headache; jaundice	Monkeys	*Aedes aegypti*	Vaccination; mosquito control
Dengue	Flavivirus (dengue virus)	Skin	Fever, muscle and joint pain, rash	Humans	*Aedes aegypti; A. albopictus*	Mosquito control
Emerging Viral Hemorrhagic Fevers (Marburg, Ebola, Lassa)	Filovirus, arenavirus	Mucous membranes	Profuse bleeding	Possibly fruit bats and other small mammals	contact with blood	None
***Hantavirus* Pulmonary Syndrome**	Bunyavirus (Sin Nombre hantavirus)	Respiratory tract	Pneumonia	Field mice	Inhalation	None

Chagas' Disease (American Trypanosomiasis)

Chagas' disease, also known as **American trypanosomiasis,** is a protozoan disease of the cardiovascular system. The causative agent is *Trypanosoma cruzi* (TRI-pa-nō-sō-mah KROOZ-ē), a flagellated protozoan (Figure 23.22). The protozoan was discovered in its insect vector by the Brazilian microbiologist Carlos Chagas in 1910. The disease occurs in Central America and parts of South America, where it chronically infects an estimated 18 million and kills as many as 50,000 annually. It has been introduced into the United States by population migration. In 2006, blood banks began screening for the disease, a practice that will identify many cases.

The reservoir for *T. cruzi* is a wide variety of wild animals, including rodents, opossums, and armadillos. The arthropod vector is the reduviid bug, called the "kissing bug" because it often bites people near the lips (see Figure 12.32d, page 352). The insects live in the cracks and crevices of mud or stone huts with thatched roofs. A recent study of reduviid bugs in the state of Arizona showed that 40% of these insects in the Tucson area harbored the parasite. The range of this insect can extend as far north as Illinois. The trypanosomes, which grow in the gut of the bug, are passed on if the bug defecates while feeding. The



Figure 23.22 *Trypanosoma cruzi,* the cause of Chagas' disease (American trypanosomiasis). The trypanosome has an undulating membrane; the flagellum follows the outer margin of the membrane and then projects beyond the body of the trypanosome as a free flagellum. Note the red blood cells in the photo.

Q Name a common trypanosomal disease that occurs in another part of the world. (*Hint*: It was discussed in Chapter 22.)

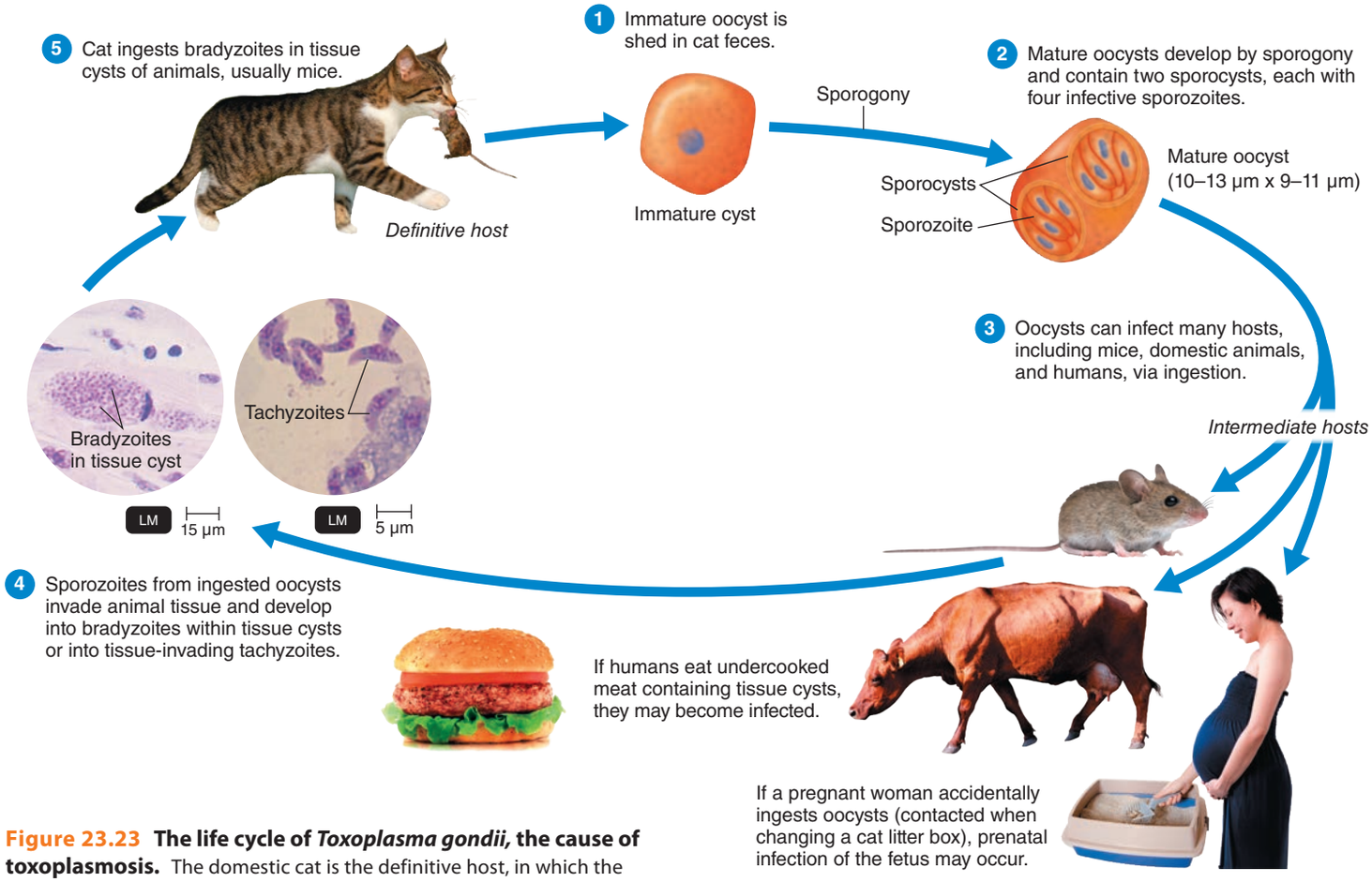


Figure 23.23 The life cycle of *Toxoplasma gondii,* the cause of toxoplasmosis. The domestic cat is the definitive host, in which the protozoa reproduce sexually.

Q How do humans contract toxoplasmosis?

bitten human or animal often rubs the feces into the bite wound or other skin abrasions by scratching or into the eye by rubbing. The infection progresses in stages. The acute stage, characterized by fever and swollen glands lasting for a few weeks, may not cause alarm. However, 20–30% of people infected will develop a chronic form of the disease—in some cases, 20 years later. Damage to the nerves controlling the peristaltic contractions of the esophagus or colon can prevent them from transporting food. This causes them to become grossly enlarged, conditions known as *megaesophagus* and *megacolon.* Most deaths are caused by damage to the heart, which occurs in about 40% of chronic cases. Pregnancy during the chronic stage can result in congenital infections.

Diagnosis in endemic areas is usually based on symptoms. In the acute phase, the trypanosomes can sometimes be detected in blood samples. During the chronic phase these are undetectable—although patients can transmit the infection by transfusions, transplants, and congenitally. Diagnosis of chronic disease depends on serological tests, which are not very sensitive or specific. Two, or even three, repeated samplings may be required.

Treating Chagas' disease is very difficult when chronic, progressive stages have been reached. The trypanosome multiplies intracellularly and is difficult to reach chemotherapeutically. The only drugs currently available are nifurtimox and benznidazole, which are triazole derivatives (see page 564). Benznidazole therapy was found to eliminate infection in about 60% of infected children and is less toxic than nifurtimox. These drugs are effective only during the early, acute phase, when few people realize they are infected, and must be administered for an extended time, 30 to 60 days. Neither drug is effective during the chronic stage; both also have serious side effects.

Toxoplasmosis

Toxoplasmosis, a disease of blood and lymphatic vessels, is caused by the protozoan *Toxoplasma gondii. T. gondii* is a spore-forming protozoan, as is the malarial parasite.

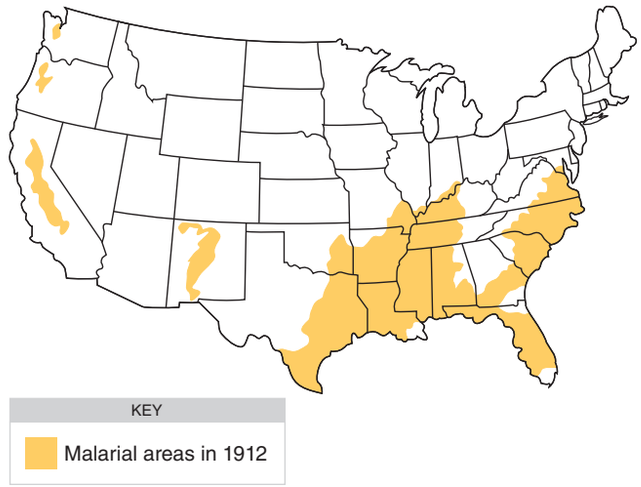
Cats are an essential part of the life cycle of *T. gondii* (**Figure 23.23**). Random tests on urban cats have shown that a large number of them are infected with the organism, which causes no apparent illness in the cat. (A curiosity of the infection in

rodents is that it apparently causes them to lose their normal avoidance behavior toward cats, making them more likely to be caught and thus to infect the cat.) The microbe undergoes its only sexual phase in the intestinal tract of the cat. Millions of oocysts are then shed in the cat's feces for 7 to 21 days and contaminate food or water that can be ingested by other animals. The *oocysts* contain *sporozoites* that invade host cells and form trophozoites called *tachyzoites* (about the size of large bacteria, 2 × 7 μm). The intracellular parasite reproduces rapidly (*tachys* is Greek for rapid). The increased numbers cause the rupture of the host cell and the release of more tachyzoites, resulting in a strong inflammatory response.

As the immune system becomes increasingly effective, the disease enters a chronic phase in animals and humans; the infected host cell develops a wall to form a *tissue cyst*. The numerous parasites within such a cyst (in this stage called *bradyzoites; bradys* being Greek for slow) reproduce very slowly, if at all, and persist for years, especially in the brain. These cysts are infective when ingested by intermediate or definitive hosts.

In people with a healthy immune system, toxoplasmosis infection results in only very mild symptoms or none at all. Some surveys have shown that approximately 22–40% of the population, without even being aware of it, eventually develops antibodies to *T. gondii* (see Figure 23.19). Humans generally acquire the infection by ingesting undercooked meats containing tachyzoites or tissue cysts, although there is a possibility of contracting the disease more directly by contact with cat feces. The primary danger is congenital infection of a fetus, resulting in stillbirth or a child with severe brain damage or vision problems. This fetal damage occurs only when the initial infection is acquired during pregnancy. As many as 4000 cases are estimated in the United States annually. The problem also affects wildlife. Off the California coast, a fatal encephalitis of sea otters has appeared, caused by *T. gondii*—apparently, they are being infected by oocysts in wastewater contaminated from the flushed contents of cat litter boxes. Loss of immune function, AIDS being the best example, allows the inapparent infection to be reactivated from tissue cysts. It often causes severe neurological impairment and may damage vision from the reactivation of tissue cysts in the eye.

Toxoplasmosis can be detected by serological tests, but interpretation is uncertain. This uncertainty is especially important because in some European countries, a person who becomes toxoplasmosis-positive during pregnancy is encouraged to abort the fetus. Recently, PCR tests have become available. If not contaminated, these tests approach an accuracy of 100%, which has revolutionized prenatal diagnosis. Toxoplasmosis can be treated with pyrimethamine in combination with sulfadiazine and folinic acid. This does not, however, affect the chronic bradyzoite stage and is quite toxic.



Areas where malaria was endemic as recently as 1912

Figure 23.24 Malaria in the United States.

Q What factors might contribute to the rise in malaria cases since 1990?

Malaria

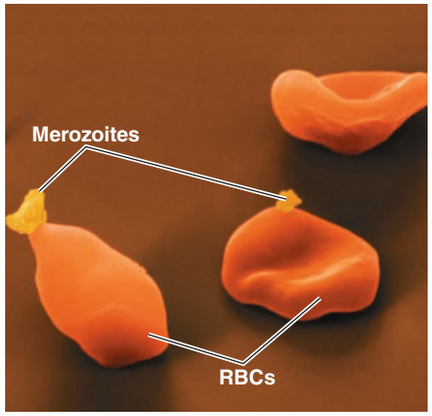
Malaria is characterized by chills and fever and often by vomiting and severe headache. These symptoms typically appear at intervals of 2 to 3 days, alternating with asymptomatic periods. Malaria occurs wherever the mosquito vector *Anopheles* is found and there are human hosts for the protozoan parasite *Plasmodium*.

The disease was once widespread in the United States (Figure 23.24), but effective mosquito control and a reduction in the number of human carriers caused the reported cases to drop below 100 by 1960. In recent years, however, there has been an upward trend in the number of U.S. cases, reflecting a worldwide resurgence of malaria, increased travel to malarial areas,

Clinical Case

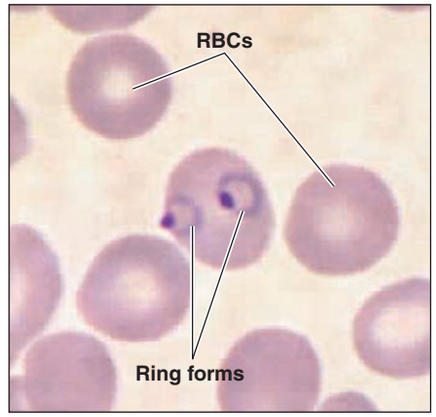
IgM antibodies are the first antibodies made in response to an infection, and they are relatively short lived. Therefore, their presence indicates a current infection. The technicians at the CDC discover that both of Katie's serum specimens are positive for dengue IgM antibodies. Dengue virus serotype 1 (DENV-1) is detected by reverse transcription polymerase chain reaction from the CSF specimen. By the time the health department interviews Katie, it is 2 weeks after she reported her original symptoms. Katie has been steadily improving since then and is now almost completely recovered.

How is dengue transmitted?



(a) Merozoites being released from lysed RBCs

SEM 1.5 μm



(b) Malarial blood smear; note the ring forms.

LM 1.5 μm

Figure 23.25 Malaria. **(a)** Some of the red blood cells (RBCs) are lysing and releasing merozoites that will infect new RBCs. **(b)** Blood smears are used in diagnosing malaria; the protozoa can be detected growing in the RBCs. In the early stages, the feeding protozoan resembles a ring within the RBC. The light central area within the circular ring is the food vacuole of the protozoan, and the dark spot on the ring is the nucleus.

Q Look at the life cycle of the malarial parasite in Figure 12.20. Which of these stages, (a) or (b), actually occurs first?

and an increase in immigration from malarial areas. Occasionally, malaria has been transmitted by unsterilized syringes used by drug addicts. Blood transfusions from people who have been in an endemic area are also a potential risk. In tropical Asia, Africa, and Central and South America, malaria is still a serious problem. It is estimated that malaria affects 300 to 500 million people worldwide and causes 2 to 4 million deaths annually. Actually, there are probably more people dying of malaria today than 30 years ago. It is returning to areas where it had been nearly eradicated, such as eastern Europe and central Asia. Africa, where 90% of the mortality from the disease occurs, suffers the most from malaria. It is estimated that it kills an African child every 30 seconds.

There are four major forms of malaria. *Plasmodium vivax* is widely distributed because it can develop in mosquitoes at a lower temperature and is the cause of the most prevalent form of malaria. Sometimes referred to as "benign" malaria, the cycle of paroxysms (recurrent intensifications of symptoms) occurs every 2 days, and the patients generally survive even without treatment. An important factor in the life cycle of *P. vivax* is that it can remain dormant in the liver of the patient for months and even years. This bridges the cold-weather gap in the life cycle of mosquitoes in temperate countries—providing them with a continuing supply of infected subjects. *P. ovale* and *P. malariae* also cause a relatively benign malaria, but even so, the victims lack energy. These latter two malarial types are lower in incidence and rather restricted geographically.

The most dangerous malaria is that caused by *P. falciparum.* Perhaps one reason for the virulence of this type of malaria is that humans and the parasite have had less time to become adapted to each other. It is believed that humans have been exposed to this parasite (through contact with birds) only in relatively recent history. Referred to as "malignant" malaria, untreated it eventually kills about half of people infected. The highest mortality rates occur in young children. More red blood cells (RBCs) are infected and destroyed than in other forms of malaria. The resulting anemia severely weakens the victim. Furthermore, the RBCs develop surface knobs that cause them to stick to the walls of the capillaries, which become clogged. This clogging prevents the infected RBCs from reaching the spleen, where phagocytic cells would eliminate them. The blocked capillaries and subsequent loss of blood supply leads to death of the tissues. Kidney and liver damage is caused in this fashion. The brain is frequently affected, and *P. falciparum* is the usual cause of cerebral malaria.

Malaria and its symptoms are intimately related to its complex reproductive cycle (see Figure 12.20, page 341). Infection is initiated by the bite of a mosquito, which carries the *sporozoite* stage of the *Plasmodium* protozoan in its saliva. About 300 to 500 sporozoites enter the bloodstream of the bitten human and within about 30 minutes enter the liver cells. The sporozoites in the liver cells undergo reproductive *schizogony* by a series of steps that finally results in the release of about 30,000 *merozoite* forms into the bloodstream.

The merozoites infect RBCs. Within the RBCs they again undergo schizogony, and after about 48 hours, the RBCs rupture and each releases about 20 new merozoites (**Figure 23.25a**). Laboratory diagnosis of malaria is usually made by examining a blood smear (Figure 23.25b) for infected RBCs. With the release of the merozoites there is also a simultaneous release of toxic compounds, which is the cause of the paroxysms of chills and fever that are characteristic of malaria. The fever reaches 40°C, and a sweating stage begins as the fever subsides. Between paroxysms, the patient feels normal.

Many of the released merozoites infect other RBCs within a few seconds to renew the cycle in the bloodstream. If only 1% of the RBCs contain parasites, an estimated 100,000,000,000 parasites will be in circulation at one time in a typical malaria patient. Some of the merozoites develop into male or female *gametocytes.* When these enter the digestive tract of a feeding mosquito, they pass through a sexual cycle that produces new infective sporozoites. It took the combined labors of several

generations of scientists to unravel this complex life cycle of the malaria parasite.

People who survive malaria acquire a limited immunity. Although they can be reinfected, they tend to have a less severe form of the disease. This relative immunity almost disappears if the person leaves an endemic area with its periodic reinfections. Malaria is especially dangerous during pregnancy because adaptive immunity is suppressed.

Malaria Vaccines

The malarial parasite reproduces in a series of stages. The number of parasites that would serve as targets for a vaccine vary greatly in these stages. The sporozoite stage involves few pathogens and was an early target for experimental vaccines. In the liver stage, the vaccine would need to deal with hundreds of pathogens. Once the parasite begins to proliferate in the blood, the numbers quickly reach into the trillions. Vaccines targeting this stage are likely only to moderate symptoms. An intriguing concept is the *transmission-blocking vaccine*. The idea is to use the human host to generate antibodies and deliver them to the biting mosquito. There, instead of dealing with trillions of parasites, the vaccine needs to deal only with the relative handful in the mosquito. Obviously, the disadvantage is that the recipients of the vaccine still get sick but would have the questionable satisfaction of knowing they are not likely to be passing it on to someone else.

In any event, large amounts of money and resources are now directed at developing a vaccine or vaccines. A truly global malarial vaccine would have to control not only *P. falciparum* but also the widespread, although milder, *P. vivax.* There are special problems in developing a malarial vaccine. For example, in its various stages, the pathogen has as many as 7000 genes that can mutate. The result is that the parasite is very efficient at evading the human immune response. The current goal is to have a vaccine that is at least 50% effective and lasts longer than a year. One such vaccine, made from a sporozoite protein produced in yeast, is in clinical trials.

Diagnosis of Malaria

The most common diagnostic test for malaria is the blood smear, which requires a microscope. It is also time-consuming and requires skill in interpretation. It is still the "gold standard" for diagnosis when a well-trained staff is available. Rapid, antigen-detecting diagnostic tests that can be performed by staff with minimal training have been developed but are relatively expensive. High-quality rapid diagnostic tests that are affordable and perform reliably under field conditions are urgently needed. In endemic areas malaria is commonly diagnosed by simply observing symptoms, mainly fever, but this frequently leads to misdiagnosis. It has been found that only about half of such patients given prescriptions for antimalarial drugs actually had the disease.

Prophylaxis and Therapy for Malaria

There are two considerations for antimalarial drugs: for prophylaxis (prevention) or for treatment.

Prophylaxis For travel to the few areas in which the malaria is still sensitive to it, chloroquine is the drug of choice. In chloroquine-resistant areas, the drug Malarone (a combination of atovaquone and proguanil) is the best tolerated. Travelers to malarial areas are often prescribed mefloquine (Lariam). It requires only a weekly dosage, but users must be cautioned about serious side effects. These include dizziness and loss of balance, which may become permanent. Some of the psychiatric symptoms, such as depression and hallucinations, may persist for years, even after the drug is no longer being used.

Therapy There is a lengthy list of antimalarial drugs available; recommendations and requirements vary with cost, likelihood of developing resistance, and other factors. In the United States (where there are about 1200 imported cases of malaria annually), if the species cannot be identified it should be assumed that the patient is infected with *P. falciparum.* If the patient is from an area still sensitive to chloroquine, it is the drug of choice; for patients coming from chloroquine-resistant zones, there are several options. The two currently preferred are malarone or oral quinine plus an antibiotic such as doxycycline.

The WHO recommends artemisinin combination therapies (ACT) for treatment of malaria worldwide. They are not used for prophylaxis. Examples of artemisinin derivatives are artesunate (not licensed in the United States) and artemether. The short-lived artemisinin component of ACT is intended to remove most of the parasites; the partner drug, with an extended period of activity, is intended to eliminate the remainder. An example of ACT is Coartem (artemether and lumefantrine).

As with other tropical diseases, the availability of medications is limited by the very low income of the people affected, which makes their development unprofitable. The most profitable application of antimalarials will probably continue to be prophylaxis of travelers to malarial areas.

Prevention

Effective control of malaria is not in sight. It will probably require a combination of vector control and chemotherapeutic and immunological approaches. Currently, the most promising preventative method is the use of insecticide-treated bed nets, because the *Anopheles* mosquito is a night feeder. In malarial areas, a sleeping room often will contain hundreds of mosquitoes, 1–5% of which are infectious. The expense of these efforts and the need for an effective political organization in malarial areas are probably going to be as important in controlling the disease as are advances in medical research.

Leishmaniasis

Leishmaniasis is a widespread and complex disease that exhibits several clinical forms. The protozoan pathogens are of about 20 different species, often categorized into three groups for reasons of simplicity. One group, *Leishmania donovani* (līsh-MAN-ē-ah DAH-nō-van-ē), causes a visceral leishmaniasis in which parasites invade the internal organs. The *L. tropica* (TROP-i-kah) and *L. braziliensis* (brah-ZIL-ē-en-sis) groups grow preferentially at cooler temperatures and cause lesions of the skin or mucous membranes. Leishmaniasis is transmitted by the bite of female sandflies, about 30 species of which are found in much of the tropical world and around the Mediterranean. These insects are smaller than mosquitoes and often penetrate the mesh of standard netting. Small mammals are an unaffected reservoir of the protozoans. The infective form, the *promastigote,* is in the saliva of the insect. It loses its flagellum when it penetrates the skin of the mammalian victim, becoming an *amastigote* that proliferates in phagocytic cells, mostly in fixed locations in tissue. These amastigotes are then ingested by feeding sandflies, renewing the cycle. Contact with contaminated blood from transfusions or shared needles can also lead to infection.

A number of cases of leishmaniasis, mostly cutaneous, have occurred among troops fighting in the Persian Gulf regions. It was once endemic in countries of southern Europe, such as Spain, Italy, Portugal, and the Balkan peninsula. Occasional cases of leishmaniasis as an opportunistic disease of HIV-infected persons are beginning to reappear in these areas.

Leishmania donovani Infection (Visceral Leishmaniasis)

Leishmania donovani infection occurs in much of the tropical world, although 90% of the cases occur in India, Bangladesh, Sudan, and Brazil. Estimates are that there are about half a million cases per year. Known as *kala azar* in India, visceral leishmaniasis is often fatal. Early symptoms, following infection by as long as a year, resemble the chills and sweating of malaria. As the protozoa proliferate in the liver and spleen, these organs enlarge greatly. Eventually, kidney function is also lost as these organs are invaded. This is a debilitating disease that, if untreated, will lead to death within a year or two.

Several inexpensive serological tests that are easy to use have been developed to diagnose visceral leishmaniasis. These have generally replaced microscopic examination of blood and tissues to demonstrate the parasite. PCR tests are very good to confirm diagnosis but usually require a central laboratory.

The primary treatment has long been injected drugs such as sodium stibogluconate that contain the toxic metal antimony. Other drugs are now replacing antimony-based preparations. The first-line treatment in Europe and United States is liposomal amphotericin B, but it's relatively expensive for endemic countries. In many of these areas, conventional formulations of amphotericin B are in use. The first effective oral drug is miltefosine. It has demonstrated a cure rate as high as 82%, but it is teratogenic, resistance develops rapidly, and it is toxic to a significant number of recipients. An inexpensive injectable aminoglycoside antibiotic, paromomycin, has shown good effectiveness.



Figure 23.26 Cutaneous leishmaniasis. Lesion on the back of the hand of a patient.

Q Is this case likely to progress to visceral leishmaniasis?

Leishmania tropica Infection (Cutaneous Leishmaniasis)

Leishmania tropica and *L. major* infection causes a cutaneous form of leishmaniasis sometimes called *oriental sore.* A papule appears at the bite site after a few weeks of incubation (**Figure 23.26**). The papule ulcerates and, after healing, leaves a prominent scar. This form of the disease is the most common and is found in much of Asia, Africa, and the Mediterranean region. It has been reported in Mexico, Central America, and the northern part of South America.

Leishmania braziliensis Infection (Mucocutaneous Leishmaniasis)

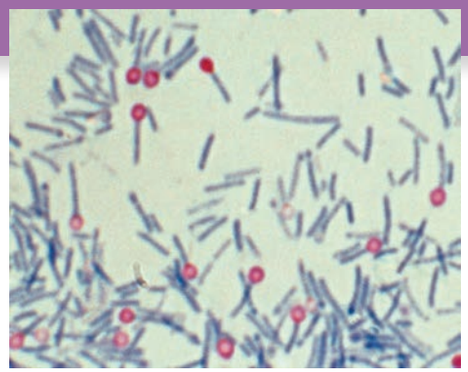
Leishmania braziliensis infection is known as mucocutaneous leishmaniasis because it affects mucous membranes as well as skin. It causes disfiguring destruction of the tissues of the nose, mouth, and upper throat. This form of leishmaniasis is most commonly found in the Yucatán Peninsula of Mexico and in the rain forest areas of Central and South America; it often affects workers harvesting the chicle sap used for making chewing gum. This disease is often referred to as *American leishmaniasis.*

Diagnosis of cutaneous and mucocutaneous leishmaniasis in the areas where they are endemic usually depends on clinical appearance and microscopic examination of the lesion scrapings.

DISEASES IN FOCUS 23.5

Infections Transmitted by Soil and Water

A minority of systemic infections are acquired by contact with soil and water. The pathogens usually enter through a break in the skin. For example, a 65-year-old man with poor circulation in his legs develops an infection following injury to a toe. Dead tissue further reduces circulation, requiring amputation of two toes. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Gram-stained bacteria from the patient's toe. LM 2.5 μm

Disease	Pathogen	Symptoms	Reservoir	Method of Transmission	Treatment
BACTERIAL DISEASE					
Gangrene	*Clostridium perfringens*	Tissue death at infection site	Soil	Puncture wound	Surgical removal of necrotic tissue
HELMINTHIC DISEASE					
Schistosomiasis	*Schistosoma* spp.	Inflammation and tissue damage at site of granulomas (e.g., liver, lungs, bladder)	Definitive host; humans	Cercariae penetrate skin	Praziquantel; oxamniquine Prevention: sanitation; elimination of host snail

Mild cases of cutaneous and mucocutaneous disease will often eventually heal, but injected antimony compounds are usually effective when required.

Babesiosis

There have been increased reports of **babesiosis,** a tickborne disease once thought to be restricted to animals. It is now a nationally notifiable disease. Rodents are the reservoir in the wild; the tick vectors are most commonly *Ixodes* species. The field of medical entomology largely arose from investigations in the nineteenth century by the American microbiologist Theobald Smith into bovine babesiosis, or tick fever, in Texas cattle. The human disease in the United States is caused by a protozoan, usually *Babesia microti.* The disease resembles malaria in some respects and has been mistaken for it; the parasites replicate in the RBCs and cause a prolonged illness of fever, chills, and night sweats. It can be much more serious, sometimes fatal, in immunocompromised patients. For example, the first human cases were observed in persons who had undergone splenectomy (removal of the spleen). Simultaneous treatment with the drugs atovaquone and azithromycin has been effective.

CHECK YOUR UNDERSTANDING

- What tickborne disease in the United States is sometimes mistaken for malaria when blood smears are inspected? **23-16**
- Eliminating which of these diseases, malaria or Chagas' disease, would have the greater effect on the well-being of the population of Africa? **23-17**

Helminthic Disease of the Cardiovascular and Lymphatic Systems

LEARNING OBJECTIVE

23-18 Diagram the life cycle of *Schistosoma,* and show where the cycle can be interrupted to prevent human disease.

Many helminths use the cardiovascular system for part of their life cycle. Schistosomes find a home there, shedding eggs that are distributed in the bloodstream. See Diseases in Focus 23.5.

Schistosomiasis

Schistosomiasis is a debilitating disease caused by a small fluke. It is probably second only to malaria in the number of people it kills or disables. The symptoms of the disease result from eggs shed by adult schistosomes in the human host. These adult helminths are 15 to 20 mm long, and the slender female lives permanently in a groove in the body of the male, from which is derived the name: *schistosome,* or split-body (**Figure 23.27a**). The union between the male and female produces a continuing supply of new eggs. Some of these eggs lodge in tissues. Defensive reactions of the human host to these foreign bodies cause local tissue damage called **granulomas** (**Figure 23.28**). Other eggs are excreted and enter the water to continue the cycle.

The life cycle of *Schistosoma* is depicted in Figure 23.27b. The disease is spread by human feces or urine carrying eggs of the

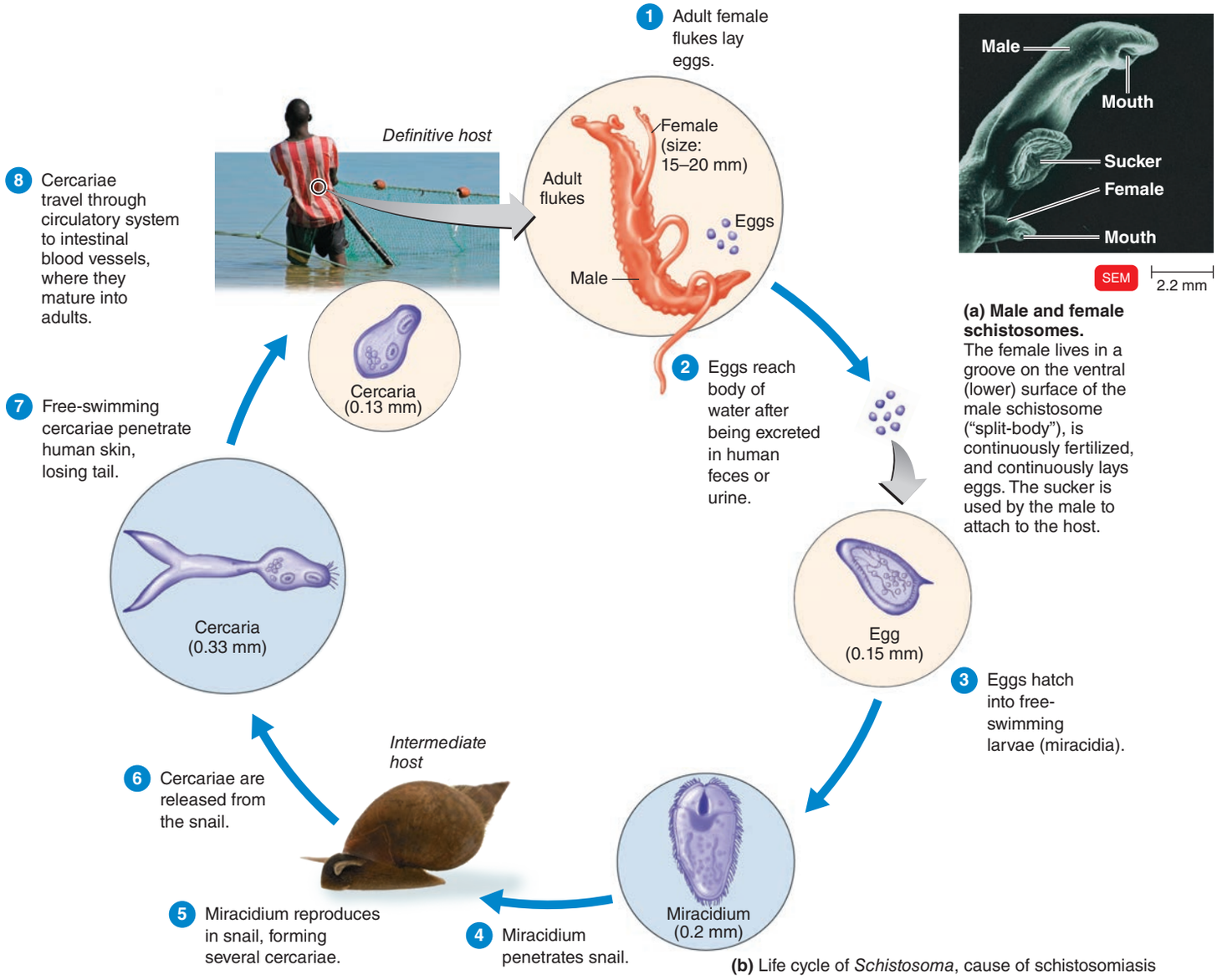


Figure 23.27 Schistosomiasis.

Q What is the role of sanitation and snails in maintaining schistosomiasis in a population?

schistosome that enter water supplies with which humans come into contact. In the developed world, sewage and water treatment minimizes the contamination of the water supply. Also, snails of certain species are essential for one stage of the life cycle of the schistosomes. They produce the cercariae that penetrate the skin of a human entering contaminated water. In most areas of the United States, a suitable host snail isn't present. Therefore, even though it's estimated that schistosome eggs are being shed by many immigrants, the disease is not being propagated.

There are three primary types of schistosomiasis. The disease caused by *Schistosoma haematobium* (shis-tō-SŌ-mah hē-mah-TŌ-bē-um), sometimes called urinary schistosomiasis, results in inflammation of the urinary bladder wall. Similarly, *S. japonicum* and *S. mansoni* cause intestinal inflammation. Depending on the species, schistosomiasis can cause damage to many different organs when eggs migrate in the bloodstream to different areas—for example, damage to the liver or lungs, urinary bladder cancer, or, when eggs lodge in the brain, neurological symptoms. Geographically, *S. japonicum* is found in east Asia. *S. haematobium* infects many people throughout Africa and the Middle East, most particularly Egypt. *S. mansoni* has a similar distribution but also is endemic in South America and the Caribbean, including Puerto Rico. It's estimated that more than 250 million of the world's population are affected.

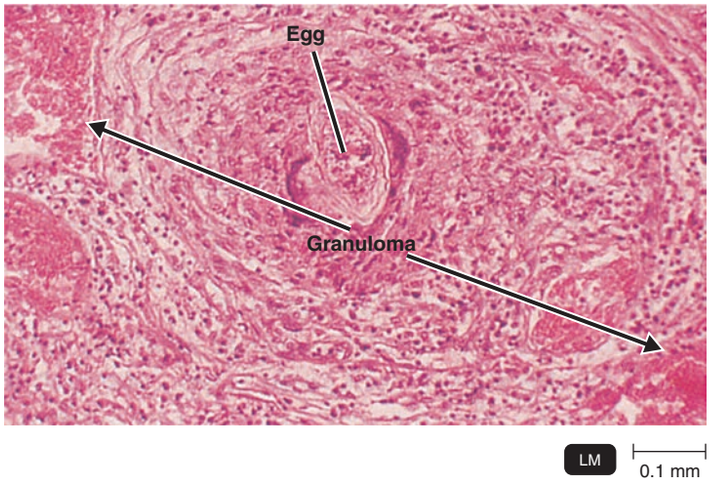


Figure 23.28 A granuloma from a patient with schistosomes. Some of the eggs laid by the adult schistosomes lodge in the tissue, and the body responds to the irritant by surrounding it with scarlike tissue, forming a granuloma.

Q Why is the immune system ineffective against adult schistosomes?

The adult worms appear to be unaffected by the host's immune system. Apparently, they quickly coat themselves with a layer that mimics the host's tissues.

Laboratory diagnosis consists of microscopic identification of the flukes or their eggs in fecal and urine specimens, intradermal tests, and serological tests such as complement-fixation and precipitin tests.

Praziquantel (primarily) and oxamniquine (only against *S. mansoni*) are approved for use against schistosomes in the United States. Sanitation and elimination of the host snail are also useful forms of control.

CHECK YOUR UNDERSTANDING

- What freshwater creature is essential to the life cycle of the pathogen causing schistosomiasis? **23-18**

Disease of Unknown Etiology

LEARNING OBJECTIVE

23-19 Recognize the clinical features of Kawasaki Syndrome.

Kawasaki Syndrome

Probably the most common cause of acquired heart disease in the United States (replacing rheumatic fever) is an acute febrile illness of unknown etiology, **Kawasaki syndrome.** As many as 4000 cases are diagnosed in the United States annually. It most often affects younger children, especially boys under the age of 5. Patients with the disease suffer a high and persistent fever, widespread skin rash, and swelling of the hands and feet and of the lymph glands in the neck. Without treatment, mortality may be about 1% but is much lower with effective treatment, involving aspirin (which affects blood clotting) and an intravenously administered immunoglobulin. Kawasaki syndrome is diagnosed primarily from its clinical signs and symptoms; there is no laboratory test available. No specific pathogen is known, and it is possible that there is an immunological cause.

CHECK YOUR UNDERSTANDING

- What diseases of the cardiovascular and lymphatic systems need to be ruled out before a clinician can conclude that a patient has Kawasaki syndrome? **23-19**

Clinical Case Resolved

Dengue is transmitted by mosquitoes. Worldwide there are 100 million cases of dengue each year. Cases of dengue in returning U.S. travelers have increased steadily during the past 20 years. Dengue is now the leading cause of acute febrile illness in U.S. travelers returning from the Caribbean, South America, and Asia. Many of these travelers are still viremic upon return to the United States and are potentially capable of introducing dengue virus into a community with competent mosquito vectors. Katie's illness, which occurred in 2009, represents the first dengue case acquired in the continental United States outside the Texas–Mexico border since 1945 and the first locally acquired case in Florida since 1934. Concern about the potential for emergence of dengue in the continental United States has increased in recent years. The most efficient mosquito vector, *Aedes aegypti,* is found in the southern and southeastern United States. A secondary vector, *A. albopictus,* has spread throughout the southeastern United States since its introduction in 1985 and was responsible for a dengue outbreak in Hawaii in 2001.

Study Outline

MasteringMicrobiology®

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Structure and Function of the Cardiovascular and Lymphatic Systems (pp. 638–639)

1. The heart, blood, and blood vessels make up the cardiovascular system.
2. Lymph, lymph vessels, lymph nodes, and lymphoid organs constitute the lymphatic system.
3. Plasma transports dissolved substances. Red blood cells carry oxygen. White blood cells are involved in the body's defense against infection.
4. Fluid that filters out of capillaries into spaces between tissue cells is called interstitial fluid.
5. Interstitial fluid enters lymph capillaries and is called lymph; vessels called lymphatics return lymph to the blood.
6. Lymph nodes contain fixed macrophages, B cells, and T cells.

Bacterial Diseases of the Cardiovascular and Lymphatic Systems (pp. 639–655)

Sepsis and Septic Shock (pp. 639–641)

1. Sepsis is an inflammatory response caused by the spread of bacteria or their toxin from a focus of infection. Septicemia is sepsis that involves proliferation of pathogens in the blood.
2. Gram-negative sepsis can lead to septic shock, characterized by decreased blood pressure. Endotoxin causes the symptoms.
3. Antibiotic-resistant enterococci and group B streptococci cause gram-positive sepsis.
4. Puerperal sepsis begins as an infection of the uterus following childbirth or abortion; it can progress to peritonitis or septicemia.
5. *Streptococcus pyogenes* is the most frequent cause of puerperal sepsis.
6. Oliver Wendell Holmes and Ignaz Semmelweiss demonstrated that puerperal sepsis was transmitted by the hands and instruments of midwives and physicians.

Bacterial Infections of the Heart (p. 641)

7. The inner layer of the heart is the endocardium.
8. Subacute bacterial endocarditis is usually caused by alpha-hemolytic streptococci, staphylococci, or enterococci.
9. The infection arises from a focus of infection, such as a tooth extraction.
10. Preexisting heart abnormalities are predisposing factors.
11. Signs include fever, anemia, and heart murmur.
12. Acute bacterial endocarditis is usually caused by *Staphylococcus aureus.*
13. The bacteria cause rapid destruction of heart valves.

Rheumatic Fever (pp. 641–642)

14. Rheumatic fever is an autoimmune complication of streptococcal infections.
15. Rheumatic fever is expressed as arthritis or inflammation of the heart. It can result in permanent heart damage.
16. Antibodies against group A beta-hemolytic streptococci react with streptococcal antigens deposited in joints or heart valves or cross-react with the heart muscle.
17. Rheumatic fever can follow a streptococcal infection, such as streptococcal sore throat. Streptococci might not be present at the time of rheumatic fever.
18. Prompt treatment of streptococcal infections can reduce the incidence of rheumatic fever.
19. Penicillin is administered as a preventive measure against subsequent streptococcal infections.

Tularemia (pp. 642–643)

20. Tularemia is caused by *Francisella tularensis.* The reservoir is small wild mammals, especially rabbits.
21. Signs include ulceration at the site of entry, followed by septicemia and pneumonia.

Brucellosis (Undulant Fever) (pp. 643–644)

22. Brucellosis can be caused by *Brucella abortus, B. melitensis,* and *B. suis.*
23. The bacteria enter through minute breaks in the mucosa or skin, reproduce in macrophages, and spread via lymphatics to liver, spleen, or bone marrow.
24. Signs include malaise and fever that spikes each evening (undulant fever).
25. Diagnosis is based on serological tests.

Anthrax (pp. 644–646)

26. *Bacillus anthracis* causes anthrax. In soil, endospores can survive for up to 60 years.
27. Grazing animals acquire an infection after ingesting the endospores.
28. Humans contract anthrax by handling hides from infected animals. The endospores enter through cuts in the skin, respiratory tract, or mouth.
29. Entry through the skin results in a pustule that can progress to sepsis. Entry through the respiratory tract can result in septic shock.
30. Diagnosis is based on isolating and identifying the bacteria.

Gangrene (p. 646)

31. Soft tissue death from ischemia (loss of blood supply) is called gangrene.
32. Microorganisms grow on nutrients released from gangrenous cells.
33. Gangrene is especially susceptible to the growth of anaerobic bacteria such as *Clostridium perfringens,* the causative agent of gas gangrene.
34. *C. perfringens* can invade the wall of the uterus during improperly performed abortions.
35. Surgical removal of necrotic tissue, hyperbaric chambers, and amputation are used to treat gas gangrene.

Systemic Diseases Caused by Bites and Scratches (pp. 646–647)

36. *Pasteurella multocida,* introduced by the bite of a dog or cat, can cause septicemia.
37. Anaerobic bacteria infect deep animal bites.
38. Cat-scratch disease is caused by *Bartonella henselae.*
39. Rat-bite fever is caused by *Streptobacillus moniliformis* and *Spirillum minus.*

Vector-Transmitted Diseases (pp. 647–655)

40. Plague is caused by *Yersinia pestis.* The vector is usually the rat flea (*Xenopsylla cheopis*).
41. Relapsing fever is caused by *Borrelia* spp. and transmitted by soft ticks.
42. Lyme disease is caused by *Borrelia burgdorferi* and is transmitted by a tick (*Ixodes*).
43. Human ehrlichiosis and anaplasmosis are caused by *Ehrlichia* and *Anaplasma* and are transmitted by *Ixodes* ticks.
44. Typhus is caused by rickettsias, obligate intracellular parasites of eukaryotic cells.

Viral Diseases of the Cardiovascular and Lymphatic Systems (pp. 655–661)

Burkitt's Lymphoma (pp. 655–656)

1. Epstein-Barr virus (EB virus, HHV-4) causes Burkitt's lymphoma.
2. Burkitt's lymphoma tends to occur in patients whose immune system has been weakened; for example, by malaria or AIDS.

Infectious Mononucleosis (pp. 656–657)

3. Infectious mononucleosis is caused by EB virus.
4. The virus multiplies in the parotid glands and is present in saliva. It causes the proliferation of atypical lymphocytes.
5. The disease is transmitted by the ingestion of saliva from infected individuals.
6. Diagnosis is made by an indirect fluorescent-antibody technique.
7. EB virus may cause other diseases, including cancers and multiple sclerosis.

Other Diseases and Epstein-Barr Virus (p. 657)

8. EB virus is associated with certain cancers and autoimmune diseases.

Cytomegalovirus Infections (p. 657)

9. CMV (HHV-5) causes intranuclear inclusion bodies and cytomegaly of host cells.
10. CMV is transmitted by saliva and other body fluids.
11. CMV inclusion disease can be asymptomatic, a mild disease, or progressive and fatal. Immunosuppressed patients may develop pneumonia.
12. If the virus crosses the placenta, it can cause congenital infection of the fetus, resulting in impaired mental development, neurological damage, and stillbirth.

Chikungunya Fever (pp. 657–660)

13. The chickungunya virus, which causes fever and severe joint pain, is transmitted by *Aedes* mosquitoes.

Classic Viral Hemorrhagic Fevers (pp. 660–661)

14. Yellow fever is caused by the yellow fever virus. The vector is the *Aedes aegypti* mosquito.
15. Signs and symptoms include fever, chills, headache, nausea, and jaundice.
16. Diagnosis is based on the presence of virus-neutralizing antibodies in the host.
17. No treatment is available, but there is an attenuated, live viral vaccine.
18. Dengue is caused by the dengue fever virus and is transmitted by the *Aedes* mosquito.
19. Signs are fever, muscle and joint pain, and rash.
20. Severe dengue is characterized by bleeding and organ failure.
21. Mosquito abatement is necessary to control the disease.

Emerging Viral Hemorrhagic Fevers (p. 661)

22. Human diseases caused by Marburg, Ebola, and Lassa fever viruses were first noticed in the late 1960s.
23. Ebola virus is found in fruit bats; Lassa fever viruses are found in rodents. Rodents are the reservoirs for Argentine and Bolivian hemorrhagic fevers.
24. *Hantavirus* pulmonary syndrome and hemorrhagic fever with renal syndrome are caused by *Hantavirus*. The virus is contracted by inhalation of dried rodent urine and feces.

Protozoan Diseases of the Cardiovascular and Lymphatic Systems (pp. 661–668)

Chagas' Disease (American Trypanosomiasis) (pp. 662–663)

1. *Trypanosoma cruzi* causes Chagas' disease. The reservoir includes many wild animals. The vector is a reduviid, the "kissing bug."

Toxoplasmosis (pp. 663–664)

2. Toxoplasmosis is caused by *Toxoplasma gondii.*
3. *T. gondii* undergoes sexual reproduction in the intestinal tract of domestic cats, and oocysts are eliminated in cat feces.
4. In the host cell, sporozoites reproduce to form either tissue-invading tachyzoites or bradyzoites.
5. Humans contract the infection by ingesting tachyzoites or tissue cysts in undercooked meat from an infected animal or contact with cat feces.
6. Congenital infections can occur. Signs and symptoms include severe brain damage or vision problems.

Malaria (pp. 664–666)

7. The signs and symptoms of malaria are chills, fever, vomiting, and headache, which occur at intervals of 2 to 3 days.
8. Malaria is transmitted by *Anopheles* mosquitoes. The causative agent is any one of four species of *Plasmodium.*
9. Sporozoites reproduce in the liver and release merozoites into the bloodstream, where they infect red blood cells and produce more merozoites.

Leishmaniasis (pp. 667–668)

10. *Leishmania* spp., which are transmitted by sandflies, cause leishmaniasis.
11. The protozoa reproduce in the liver, spleen, and kidneys.
12. Antimony compounds are used for treatment.

Babesiosis (p. 668)

13. Babesiosis is caused by the protozoan *Babesia microti* and is transmitted to humans by ticks.

Helminthic Disease of the Cardiovascular and Lymphatic Systems (pp. 668–670)

Schistosomiasis (pp. 668–670)

1. Species of the blood fluke *Schistosoma* cause schistosomiasis.
2. Eggs eliminated with feces hatch into larvae that infect the intermediate host, a snail. Free-swimming cercariae are released from the snail and penetrate the skin of a human.
3. The adult flukes live in the veins of the liver or urinary bladder in humans.
4. Granulomas are from the host's defense to eggs that remain in the body.
5. Observation of eggs or flukes in feces, skin tests, or indirect serological tests may be used for diagnosis.
6. Chemotherapy is used to treat the disease; sanitation and snail eradication are used to prevent it.

Disease of Unknown Etiology (p. 670)

Kawasaki Syndrome (p. 670)

1. Kawasaki syndrome is characterized by fever, rash, and swollen lymph nodes in the neck. The cause is unknown.

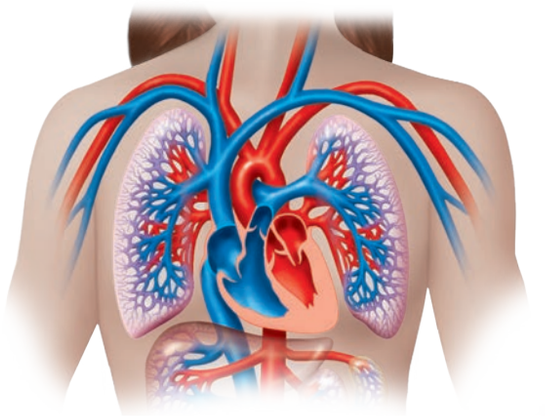
Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. DRAW IT Show the path of *Streptococcus* from a focal infection to the pericardium. Identify the portals of entry for *Trypanosoma cruzi, Hantavirus,* and cytomegalovirus.



2. Complete the following table.

Disease	Frequent Causative Agent	Predisposing Condition(s)
Puerperal sepsis		
Subacute bacterial endocarditis		
Acute bacterial endocarditis		
Rheumatic fever		

3. Compare and contrast epidemic typhus, endemic murine typhus, and tickborne typhus.
4. Complete the following table.

Disease	Causative Agent	Vector	Treatment
Malaria			
Yellow fever			
Dengue			
Relapsing fever			
Leishmaniasis			

5. Complete the following table.

Disease	Causative Agent	Transmission	Reservoir
Tularemia			
Brucellosis			
Anthrax			
Lyme disease			
Ehrlichiosis			
Cytomegalic inclusion disease			
Plague			

6. List the causative agent, method of transmission, and reservoir for schistosomiasis, toxoplasmosis, and Chagas' disease. Which disease are you most likely to get in the United States? Where are the other diseases endemic?
7. Compare and contrast cat-scratch disease and toxoplasmosis.
8. Why is *Clostridium perfringens* likely to grow in gangrenous wounds?
9. List the causative agent and method of transmission of infectious mononucleosis.
10. NAME IT Most people have been infected with this microorganism, often without symptoms. Infection during pregnancy can result in deafness or mental retardation in the newborn.

Multiple Choice

Use the following choices to answer questions 1 through 4:

a. ehrlichiosis
b. Lyme disease
c. septic shock
d. toxoplasmosis
e. viral hemorrhagic fever

1. A patient presents with vomiting, diarrhea, and a history of fever and headache. Bacterial cultures of blood, CSF, and stool are negative. What is your diagnosis?
2. A patient was hospitalized because of continuing fever and progression of symptoms including headache, fatigue, and back pain. Tests for antibodies to *Borrelia burgdorferi* were negative. What is your diagnosis?
3. A patient complained of headache. A CT (computed tomography) scan revealed cysts of varying size in her brain. What is your diagnosis?
4. A patient presents with mental confusion, rapid breathing and heart rate, and low blood pressure. What is your diagnosis?
5. A patient has a red circular rash on his arm and fever, malaise, and joint pain. The most appropriate treatment is
   a. antibiotics.
   b. chloroquine.
   c. anti-inflammatory drugs.
   d. antimony.
   e. no treatment.
6. Which of the following is not a tickborne disease?
   a. babesiosis
   b. ehrlichiosis
   c. Lyme disease
   d. relapsing fever
   e. tularemia

Use the following choices to answer questions 7 and 8:

a. brucellosis
b. malaria
c. relapsing fever
d. Rocky Mountain spotted fever
e. Ebola hemorrhagic fever

7. The patient's fever spikes each evening. Oxidase-positive, gram-negative coccobacilli were isolated from a lesion on his arm. What is your diagnosis?
8. The patient was hospitalized with fever and headache. Spirochetes were observed in her blood. What is your diagnosis?
9. Which of these diseases has the highest incidence in the U.S.?
   a. brucellosis
   b. Ebola hemorrhagic fever
   c. malaria
   d. plague
   e. Rocky Mountain spotted fever
10. Nineteen workers in a slaughterhouse developed fever and chills, with the fever spiking to 40°C each evening. The most likely method of transmission of this disease is
    a. a vector.
    b. the respiratory route.
    c. a puncture wound.
    d. an animal bite.
    e. water.

Analysis

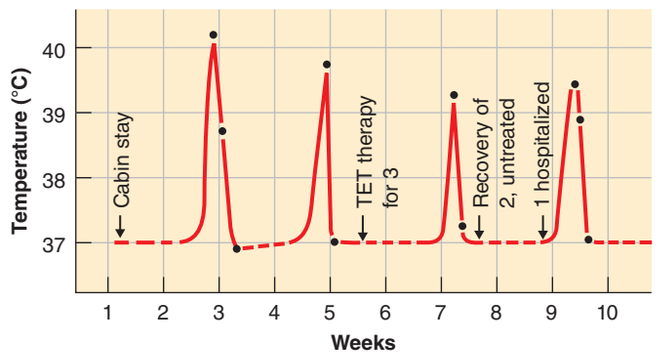
1. Indirect fluorescent-antibody (FA) tests on the serum of three 25-year-old women, each of whom is considering pregnancy, provided the information below. Which of these women may have toxoplasmosis? What advice might be given to each woman with regard to toxoplasmosis?

	Antibody Titer		
Patient	**Day 1**	**Day 5**	**Day 12**
Patient A	1024	1024	1024
Patient B	1024	2048	3072
Patient C	0	0	0

2. What is the most effective way to control malaria and dengue?
3. In adults, the second dengue virus infection results in severe dengue, characterized by bleeding from the skin and mucosa. In infants under 1 year old, the first dengue virus infection results in severe dengue. Offer an explanation for this.

Clinical Applications and Evaluation

1. A 19-year-old man went deer hunting. While on the trail, he found a partially dismembered dead rabbit. The hunter picked up the front paws for good luck charms and gave them to another hunter in the party. The rabbit had been handled with bare hands that were bruised and scratched from the hunter's work as an automobile mechanic. Festering sores on his hands, legs, and knees were noted 2 days later. What infectious disease do you suspect the hunter has? How would you proceed to prove it?
2. On March 30, a 35-year-old veterinarian experienced fever, chills, and vomiting. On March 31, he was hospitalized with diarrhea, left armpit bubo, and secondary bilateral pneumonia. On March 27, he had treated a cat that had labored respiration; an X-ray image revealed pulmonary infiltrates. The cat died on March 28 and was disposed of. Chloramphenicol was administered to the veterinarian. On April 10, his temperature returned to normal, and on April 20, he was released from the hospital. Sixty human contacts were given tetracycline. Identify the incubation and prodromal periods for this case. Explain why the 60 contacts were treated. What was the etiologic agent? How would you identify the agent?
3. Three of five patients who underwent heart valve replacement surgery developed bacteremia. The causative agent was *Enterobacter cloacae.* What were the patients' signs and symptoms? How would you identify this bacterium? A manometer used in the operations was culture-positive for *E. cloacae.* What is the most likely source of this contaminant? Suggest a way of preventing such occurrences.
4. In August and September, six people who each at different times spent a night in the same cabin developed fever, as shown in the graph below. Three recovered after tetracycline (TET) therapy, two recovered without therapy, and one was hospitalized with septic shock. What is the disease? What is the incubation period of this disease? How do you account for the periodic temperature changes? What caused septic shock in the sixth patient?



5. A 67-year-old man worked in a textile mill that processed imported goat hair into fabrics. He noticed a painless, slightly swollen pimple on his chin. Two days later he developed a 1-cm ulcer at the pimple site and a temperature of 37.6°C. He was treated with tetracycline. What is the etiology of this disease? Suggest ways to prevent it.



In the Clinic

As a nurse educator in a large urban hospital, you are asked to provide flu classes for patients and staff. Differentiate influenza from the common cold. **What prevention measures will you recommend to your students?**

Hint: Read about the common cold on page 680 and influenza on page 695.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

24 Microbial Diseases of the Respiratory System

With every breath, we inhale several microorganisms; therefore, the upper respiratory system is a major portal of entry for pathogens. In fact, respiratory system infections are the most common type of infection—and among the most damaging. Some pathogens that enter via the respiratory route can infect other parts of the body, causing such diseases as measles, mumps, and rubella.

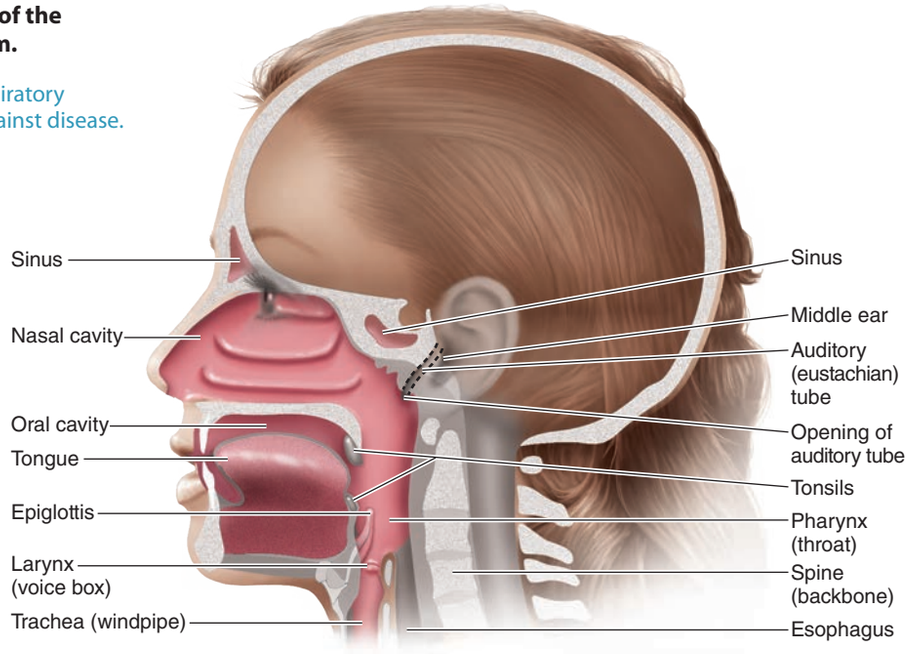
The upper respiratory system has several anatomical defenses against airborne pathogens. Coarse hairs in the nose filter large dust particles from the air. The nose is lined with a mucous membrane that contains numerous mucus-secreting cells and cilia. The upper portion of the throat also contains a ciliated mucous membrane. The mucus moistens inhaled air and traps dust and microorganisms. The cilia help remove these particles by moving them toward the mouth for elimination.

At the junction of the nose and throat are masses of lymphoid tissue, the tonsils, which contribute immunity to certain infections. Because the nose and throat are connected to the sinuses, nasolacrimal apparatus, and middle ear, infections commonly spread from one region to another. Microbes that escape these defenses may be able to cause infection. Such an infection caused by the *Chlamydophila psittaci* shown in the photograph is described in the Clinical Case in this chapter.

When infecting a host cell, *Chlamydia* bacteria produce noninfectious-reticulate bodies (brown) and infectious elementary bodies (red).

Figure 24.1 Structures of the upper respiratory system.

Q Name the upper respiratory system's defenses against disease.



Structure and Function of the Respiratory System

LEARNING OBJECTIVE

24-1 Describe how microorganisms are prevented from entering the respiratory system.

It's convenient to think of the respiratory system as being composed of two divisions: the upper respiratory system and the lower respiratory system. The **upper respiratory system** consists of the nose, the pharynx (throat), and the structures associated with them, including the middle ear and the auditory (eustachian) tubes (Figure 24.1). Ducts from the sinuses and the nasolacrimal ducts from the lacrimal (tear-forming) apparatus empty into the nasal cavity (see Figure 16.2, page 443). The auditory tubes from the middle ear empty into the upper portion of the throat.

The **lower respiratory system** consists of the larynx (voice box), trachea (windpipe), bronchial tubes, and *alveoli* (Figure 24.2). Alveoli are air sacs that make up the lung tissue; within them, oxygen and carbon dioxide are exchanged between the lungs and blood. Our lungs contain more than 300 million alveoli, with an area for gas exchange of 70 or more square meters in an average adult. The double-layered membrane enclosing the lungs is the *pleura*, or pleural membranes. A ciliated mucous membrane lines the lower respiratory system down to the smaller bronchial tubes and helps prevent microorganisms from reaching the lungs.

Particles trapped in the larynx, trachea, and larger bronchial tubes are moved up toward the throat by a ciliary action called the *ciliary escalator* (see Figure 16.3, page 444). If microorganisms actually reach the lungs, phagocytic cells called *alveolar macrophages* usually locate, ingest, and destroy most of them. IgA antibodies in such secretions as respiratory mucus, saliva, and tears also help protect mucosal surfaces of the respiratory system from many pathogens. Thus, the body has several mechanisms for removing the pathogens that cause airborne infections.

CHECK YOUR UNDERSTANDING

What is the function of hairs in the nasal passages? **24-1**

Clinical Case: It's for the Birds

For the past 2 days, Caille Nguyen has had a fever and feels out of sorts. In fact, her entire family is sick. Her three children, Gabbie, Steven, and Tre, also have fevers. Caille's husband, Art, and Gabbie and Steven have no appetite and are beginning to lose weight. Everyone has a dry cough. At first Caille thinks the children are just sad because of the loss of Bitsy, their beloved cockatiel. The family had purchased the cockatiel from a local pet store 2 months earlier. Unfortunately, Bitsy had an increasingly difficult time breathing and could not stand erect; she had to be euthanized by a local veterinarian the week before.

What could be causing the Nguyen family's symptoms? Read on to find out.

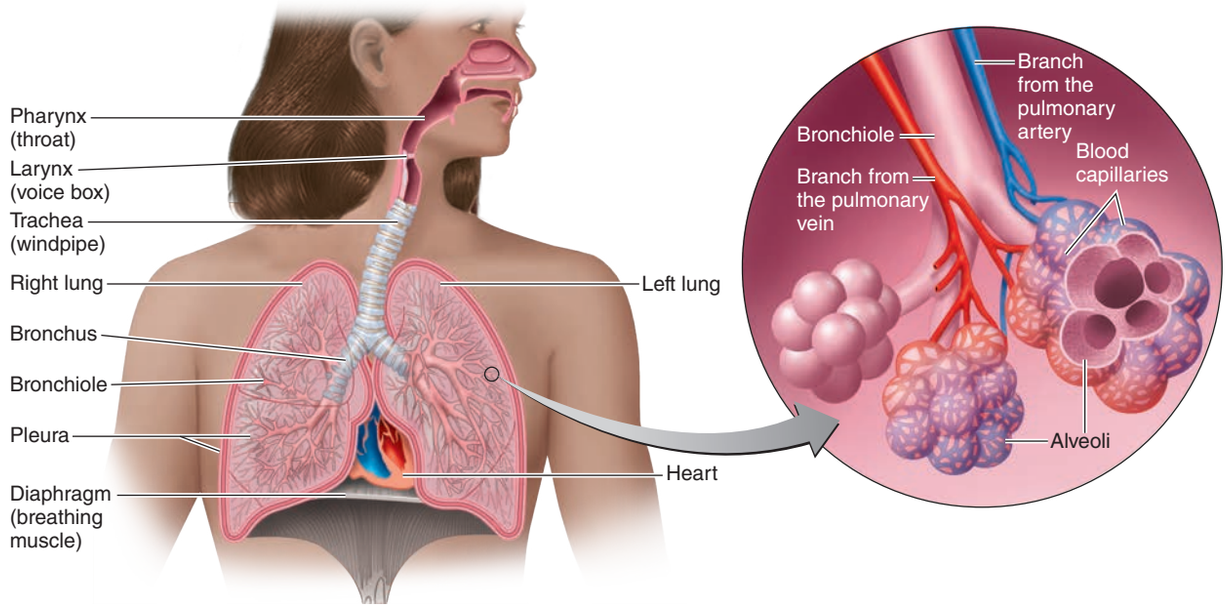


Figure 24.2 Structures of the lower respiratory system.

Q Name the lower respiratory system's defenses against disease.

Normal Microbiota of the Respiratory System

LEARNING OBJECTIVE

24-2 Characterize the normal microbiota of the upper and lower respiratory systems.

A number of potentially pathogenic microorganisms are part of the normal microbiota in the upper respiratory system. However, they usually do not cause illness because the predominant microorganisms of the normal microbiota suppress their growth by competing with them for nutrients and producing inhibitory substances.

By contrast, the lower respiratory tract is nearly sterile—although the trachea may contain a few bacteria—because of the normally efficient functioning of the ciliary escalator in the bronchial tubes.

CHECK YOUR UNDERSTANDING

✓ Normally, the lower respiratory tract is nearly sterile. What is the primary mechanism responsible? **24-2**

Microbial Diseases of the Upper Respiratory System

LEARNING OBJECTIVE

24-3 Differentiate pharyngitis, laryngitis, tonsillitis, sinusitis, and epiglottitis.

As most of us know from personal experience, the respiratory system is the site of many common infections. We will soon discuss **pharyngitis,** inflammation of the mucous membranes of the throat, or sore throat. When the larynx is the site of infection, we suffer from **laryngitis,** which affects our ability to speak. The microbes that cause pharyngitis also can cause inflamed tonsils, or **tonsillitis.**

The nasal sinuses are cavities in certain cranial bones that open into the nasal cavity. They have a mucous membrane lining that is continuous with that of the nasal cavity. Infection of a sinus involving heavy nasal discharge of mucus is called **sinusitis.** If the opening by which the mucus leaves the sinus becomes blocked, internal pressure can cause pain or a sinus headache. These diseases are almost always *self-limiting,* meaning that recovery will usually occur even without medical intervention.

Probably the most threatening infectious disease of the upper respiratory system is **epiglottitis,** inflammation of the epiglottis. The epiglottis is a flaplike structure of cartilage that prevents ingested material from entering the larynx (see Figure 24.1). Epiglottitis is a rapidly developing disease that can result in death within a few hours. It is caused by opportunistic pathogens, usually *Haemophilus influenzae* type b. The Hib vaccine, although directed primarily at meningitis (page 610),

has significantly reduced the incidence of epiglottitis in the vaccinated population.

CHECK YOUR UNDERSTANDING

Which one of the following is most likely to be associated with a headache: pharyngitis, laryngitis, sinusitis, or epiglottitis? **24-3**

Bacterial Diseases of the Upper Respiratory System

LEARNING OBJECTIVE

24-4 List the causative agent, symptoms, prevention, preferred treatment, and laboratory identification tests for streptococcal pharyngitis, scarlet fever, diphtheria, cutaneous diphtheria, and otitis media.

Airborne pathogens make their first contact with the body's mucous membranes as they enter the upper respiratory system. Many respiratory or systemic diseases initiate infections here.

Streptococcal Pharyngitis (Strep Throat)

Streptococcal pharyngitis (strep throat) is an upper respiratory infection caused by *group A streptococci (GAS)*. This gram-positive bacterial group consists solely of *Streptococcus pyogenes,* the same bacterium responsible for many skin and soft tissue infections, such as impetigo, erysipelas, and acute bacterial endocarditis.

Pharyngitis is characterized by local inflammation and a fever (**Figure 24.3**). Frequently, tonsillitis occurs, and the lymph nodes in the neck become enlarged and tender. Another frequent complication is otitis media (see page 679).

The pathogenicity of GAS is enhanced by their resistance to phagocytosis. They are also able to produce special enzymes, called *streptokinases,* which lyse fibrin clots, and *streptolysins,* which are cytotoxic to tissue cells, red blood cells, and protective leukocytes.



Figure 24.3 Streptococcal pharyngitis. Note the inflammation.

How is strep throat diagnosed?

At one time, the diagnosis of pharyngitis was based on culturing bacteria from a throat swab. Results took overnight or longer, but, beginning in the early 1980s, rapid antigen detection tests that were capable of detecting GAS directly on throat swabs became available. The first rapid tests used latex indirect agglutination methods (see Figure 18.7, page 505). These have been generally replaced by **enzyme immunoassay (EIA)** tests that are more sensitive and easier to read. Currently, there is a wide range of rapid tests commercially available to evaluate cases of pharyngitis, which reflects the fact that millions of patients seek care for it every year. Actually, the majority of patients seen for sore throats do not have a streptococcal infection. Some cases are caused by other bacteria, but many are caused by viruses—for which antibiotic therapy is ineffective. Even the presence of GAS is not a conclusive indication that it is responsible for the sore throat. In areas where acute rheumatic fever occurs the recommendation is to use both bacterial culture and rapid tests. Fortunately, GAS have remained sensitive to penicillin, although some resistance to erythromycin has appeared.

Pharyngitis is now most commonly transmitted by respiratory secretions, but epidemics of streptococcal pharyngitis spread by unpasteurized milk were once frequent.

Scarlet Fever

When the *Streptococcus pyogenes* strain causing streptococcal pharyngitis produces an *erythrogenic* (reddening) *toxin,* the resulting infection is called **scarlet fever.** When the strain produces this toxin, it has been lysogenized by a bacteriophage (see Figure 13.12, page 371). Recall that this means the genetic information of a bacteriophage (bacterial virus) has been incorporated into the chromosome of the bacterium, so the characteristics of the bacterium have been altered. The toxin causes a pinkish red skin rash, which is probably the skin's hypersensitivity reaction to the circulating toxin, and a high fever. The tongue has a spotted, strawberry-like appearance and then, as it loses its upper membrane, becomes very red and enlarged. Classically, scarlet fever has been considered to be associated with streptococcal pharyngitis, but it might accompany a streptococcal skin infection.

The incidence of scarlet fever has varied over time in severity and frequency. Today it is a relatively mild and rare disease.

Diphtheria

Another bacterial infection of the upper respiratory system is **diphtheria.** Until 1935, it was the leading infectious killer of children in the United States. The disease begins with a sore throat and fever, followed by general malaise and swelling of the neck. The organism responsible is *Corynebacterium diphtheriae,* a gram-positive, non–endospore-forming rod. Its morphology is pleomorphic, frequently club-shaped, and it stains unevenly (**Figure 24.4**).

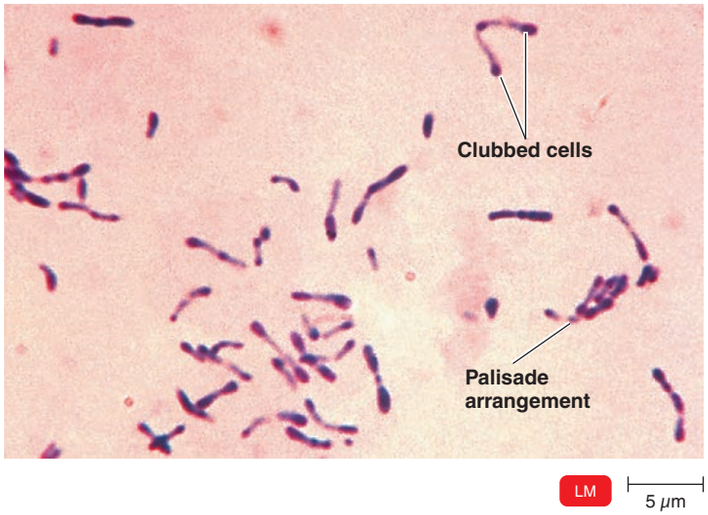


Figure 24.4 ***Corynebacterium diphtheriae,* the cause of diphtheria.** This Gram stain shows the club-shaped morphology; the dividing cells are often observed folding together to form V- and Y-shaped figures. Also notice the side-by-side palisade arrangement.

Q Are corynebacteria gram-positive or gram-negative?

Part of the normal immunization program for children in the United States is the **DTaP vaccine,** which protects against diphtheria, tetanus, and pertussis. In this name, the D represents diphtheria toxoid, an inactivated toxin that causes the body to produce antibodies against the diphtheria toxin. For more information on this vaccine, see the **Big Picture** feature on pertussis on pages 682–683.

C. diphtheriae has adapted to a generally immunized population, and relatively nonvirulent strains are found in the throats of many symptomless carriers. The bacterium is well suited to droplet transmission and is very resistant to drying.

A tough grayish membrane that forms in the throat in response to the infection is characteristic of diphtheria (from the Greek word for leather). It contains fibrin, dead tissue, and bacterial cells and can totally block the passage of air to the lungs.

Although the bacteria don't invade tissues, those that have been lysogenized by a phage can produce a powerful exotoxin, which then circulates in the bloodstream and interferes with protein synthesis. Historically, diphtheria was the first disease for which a toxic cause was identified. Only 0.01 mg of this highly virulent toxin can be fatal. Thus, if antitoxin therapy is to be effective, it must be administered before the toxin enters the tissue cells. When such organs as the heart and kidneys are affected by the toxin, the disease can rapidly be fatal. In other cases the nerves can be involved, and partial paralysis results.

The number of diphtheria cases reported in the United States each year is currently five or fewer. In young children, the disease occurs mainly in groups that have not been immunized for religious or other reasons. When diphtheria was more common, repeated contacts with toxigenic strains reinforced the immunity, which otherwise weakens with time. Many adults now lack immunity because routine immunization was less available during their childhood. Some surveys indicate effective immune levels in as few as 20% of the adult population. In the United States, when any trauma in adults requires tetanus toxoid, it is usually combined with diphtheria toxoid (Td vaccine).

Diphtheria is also expressed as **cutaneous diphtheria.** In this form of the disease, *C. diphtheriae* infects the skin, usually at a wound or similar skin lesion, and there is minimal systemic circulation of the toxin. In cutaneous infections, the bacteria cause slow-healing ulcerations that are covered by a gray membrane. Cutaneous diphtheria is fairly common in tropical countries.

In the past, diphtheria was spread mainly to healthy carriers by droplet infection. Respiratory cases have been known to arise from contact with cutaneous diphtheria.

Laboratory diagnosis by bacterial identification is difficult, requiring several selective and differential media. Identification is complicated by the need to differentiate toxin-forming isolates from strains that are not toxigenic; both may be found in the same patient.

Even though antibiotics such as penicillin and erythromycin control the growth of the bacteria, they do not neutralize the diphtheria toxin. Thus antibiotics should be used only in conjunction with antitoxin.

CHECK YOUR UNDERSTANDING

✓ Among streptococcal pharyngitis, scarlet fever, or diphtheria, which two diseases are usually caused by the same genus of bacteria? **24-4**

Otitis Media

One of the more uncomfortable complications of the common cold, or of any infection of the nose or throat, is infection of the middle ear, **otitis media,** or earache. The pathogens cause the formation of pus, which builds up pressure against the eardrum and causes it to become inflamed and painful (**Figure 24.5**). The condition is most frequent in early childhood because the auditory tube connecting the middle ear to the throat is small and more horizontal than in adults and so is more easily blocked by infection (see Figure 24.1).

A number of bacteria can cause otitis media. The most commonly isolated pathogen is *S. pneumoniae* (about 35% of cases). Other bacteria frequently involved are nonencapsulated *H. influenzae* (20–30%), *Moraxella catarrhalis* (more-ax-EL-lah ka-TAR-ra-lis) (10–15%), *S. pyogenes* (8–10%), and *S. aureus* (1–2%). In about 3–5% of cases, no bacteria can be detected. Viral infections may be responsible in these instances; respiratory syncytial viruses (see page 695) are the most common isolate.

Otitis media affects 85% of children before the age of 3 and accounts for nearly half of office visits to pediatricians—an estimated 8 million cases each year in the United States. Treatment always assumes that bacteria are the cause, and it is estimated that ear infections account for about one-fourth of the prescriptions

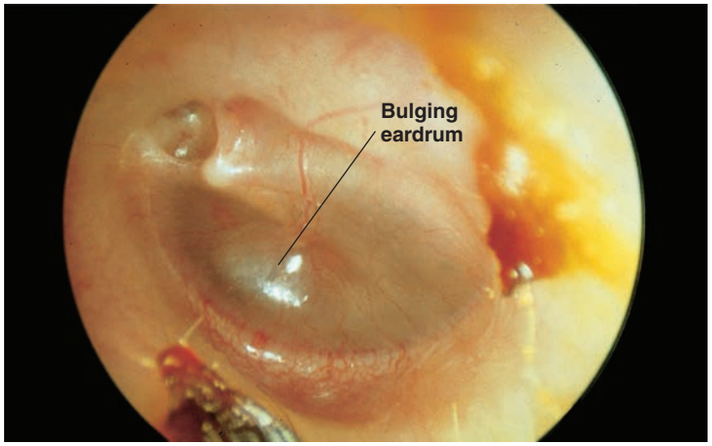


Figure 24.5 Acute otitis media, with bulging eardrum.

Q What is the most common bacterium causing middle ear infections?

for antibiotics. Broad-spectrum penicillins, such as amoxicillin, are usually the first choice for children. Many physicians now question the value of antibiotics, uncertain whether these drugs shorten the course of the disease. A conjugate vaccine exists that is intended to prevent pneumonia caused by *S. pneumoniae.* Experience so far has shown that the vaccine has the welcome side effect of reducing the incidence of otitis media by 6–7%. This reduction may not sound like much, but it amounts to over a million fewer cases every year.

Viral Disease of the Upper Respiratory System

LEARNING OBJECTIVE

24-5 List the causative agents and treatments for the common cold.

Probably the most prevalent disease of humans, at least those living in the temperate zones, is a viral disease affecting the upper respiratory system—the common cold.

The Common Cold

More than one virus is involved in the etiology of the **common cold.** In fact, there are hundreds—more than 200 different viruses that are members of several different families of viruses are known to cause colds. Identification procedures that require isolation and culturing often fail to identify the cause of a cold. However, new techniques that use PCR to look for the viral DNA or RNA make culturing unnecessary and frequently turn up previously unknown cold viruses. Most cold viruses are rhinoviruses (30–50%); coronaviruses (10–15%) are also important. However, 20–30% of viruses that cause colds are classified by researchers as previously unknown.

We tend to accumulate immunities against cold viruses during our lifetime, which may be a reason why older people usually have fewer colds. Immunity is based on the ratio of IgA antibodies to single serotypes and has a good short-term effectiveness. Isolated populations may develop a group immunity, and colds disappear among them until a new set of viruses is introduced.

The symptoms of the common cold are familiar to all of us. They include sneezing, excessive nasal secretion, and congestion. The infection can easily spread from the throat to the sinuses, the lower respiratory system, and the middle ear, leading to complications of laryngitis and otitis media. The uncomplicated cold usually is not accompanied by fever. It is generally in the interest of a cold-causing virus not to make the cold sufferer too ill—the host needs to move around, shedding the virus to others, especially in mucus.

Rhinoviruses thrive at a temperature slightly below that of normal body temperature, such as might be found in the upper respiratory system, which is open to the outside environment. No one knows exactly why the number of colds seems to increase with colder weather in temperate zones. It is not known whether closer indoor contact promotes epidemic-type transmission or whether physiological changes increase susceptibility.

A single rhinovirus deposited on the nasal mucosa is often sufficient to cause a cold. However, there is surprisingly little agreement on how the cold virus is transmitted to a site in the nose. Experiments with guinea pigs and the influenza virus show that viruses tend to be carried on airborne droplets of water vapor. In the dry air (low humidity) typical of low temperatures, the droplets are smaller and remain airborne longer, facilitating person-to-person transmission. At the same time, the cooler air causes the cilia of the ciliary escalator to work more slowly, allowing inhaled viruses to spread in the upper respiratory system.

Research has shown that during the first 3 days of a cold, nasal mucus contains a high concentration of cold viruses that multiply in nasal cells. (If mucus is green, the reason is that it contains many white blood cells with iron-containing components directed at destroying pathogens.) The viruses in mucus remain viable on surfaces touched by contaminated fingers for at least several hours. The conventional wisdom is that the virus is most likely transmitted through finger contact with the nostrils and eyes (tear ducts communicate with the nose). Transmission also occurs when the cold viruses in airborne droplets from coughing and sneezing land on suitable tissues in the nose and eyes.

Because colds are caused by viruses, antibiotics are of no use in treatment. Symptoms can be relieved by cough suppressants and antihistamines, but these medications do not speed recovery. There is still considerable truth in the medical adage that an untreated cold will run its normal course to recovery in a week, whereas with treatment it will take 7 days.

The diseases affecting the upper respiratory system are summarized in Diseases in Focus 24.1.

CHECK YOUR UNDERSTANDING

✓ Which viruses, rhinoviruses or coronaviruses, cause about half of the cases of the common cold? **24-5**

DISEASES IN FOCUS 24.1

Microbial Diseases of the Upper Respiratory System

The differential diagnosis for the following diseases is usually based on clinical symptoms, and throat swabs may be used to culture bacteria. For example, a patient presents with fever and a red, sore throat. Later a grayish membrane appears in the throat. Gram-positive rods were cultured from the membrane. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Grayish membrane in the throat is a characteristic of this disease.

Disease	Pathogen	Symptoms	Treatment
BACTERIAL DISEASES			
Epiglottitis	*Haemophilus influenzae*	Inflammation of the epiglottis	Antibiotics; maintain airway Prevention: Hib vaccine
Streptococcal Pharyngitis (strep throat)	Streptococci, especially *Streptococcus pyogenes*	Inflamed mucous membranes of the throat	Penicillin
Scarlet Fever	Erythrogenic toxin-producing strains of *Streptococcus pyogenes*	Streptococcal exotoxin causes reddening of skin and tongue and peeling of affected skin	Penicillin
Diphtheria	*Corynebacterium diphtheriae*	Grayish membrane forms in throat; cutaneous form also occurs	Penicillin and antitoxin Prevention: DTaP vaccine
Otitis Media	Several agents, especially *Staphylococcus aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae*	Accumulations of pus in middle ear cause painful pressure on eardrum	Broad-spectum antibiotics Prevention: pneumococcal vaccine
VIRAL DISEASE			
Common Cold	Rhinoviruses, coronaviruses	Familiar symptoms of coughing, sneezing, runny nose	Supportive

Microbial Diseases of the Lower Respiratory System

Many of the same bacteria and viruses that infect the upper respiratory system can also infect the lower respiratory system. As the bronchi become involved, **bronchitis** or **bronchiolitis** develops (see Figure 24.2). A severe complication of bronchitis is **pneumonia,** in which the pulmonary alveoli become involved.

Bacterial Diseases of the Lower Respiratory System

LEARNING OBJECTIVES

24-6 List the causative agent, symptoms, prevention, preferred treatment, and laboratory identification tests for pertussis and tuberculosis.

24-7 Compare and contrast the seven bacterial pneumonias discussed in this chapter.

24-8 List the etiology, method of transmission, and symptoms of melioidosis.

Bacterial diseases of the lower respiratory system include tuberculosis and the many types of pneumonia caused by bacteria. Lesser-known diseases such as psittacosis and Q fever also fall into this category.

Pertussis (Whooping Cough)

Infection by the bacterium *Bordetella pertussis* results in **pertussis,** or **whooping cough.** *B. pertussis* is a small, obligately aerobic, gram-negative coccobacillus. The virulent strains possess a capsule. The bacteria attach specifically to ciliated cells in the trachea, first impeding their ciliary action and then progressively destroying the cells (Figure 24.6). This prevents the ciliary escalator system from moving mucus. *B. pertussis* produces several toxins. *Tracheal cytotoxin,* a fixed cell wall fraction of the

BIG PICTURE

Pertussis

After falling for decades, pertussis cases began to rise again in the 1990s, peaking at over 48,000 cases in a 2012 U.S. epidemic. Why?

The Public Health Triumph of Pertussis Vaccines

Before vaccines existed, nearly every child in the United States contracted pertussis, with hundreds of thousands of infections occurring each year. About 6000 people died annually, mostly children under age 5. Those who survived experienced lifelong immunity.

Desire for a Safer Vaccine

The pertussis component of DTP was originally a whole-cell, heat-killed vaccine. DTP was very effective, conferring excellent long-term immunity. But manufacture of any whole-cell vaccine carries risk of an error in the process that kills bacteria. A batch of vaccine containing live bacteria can cause infections, rather than the desired immune response without illness.

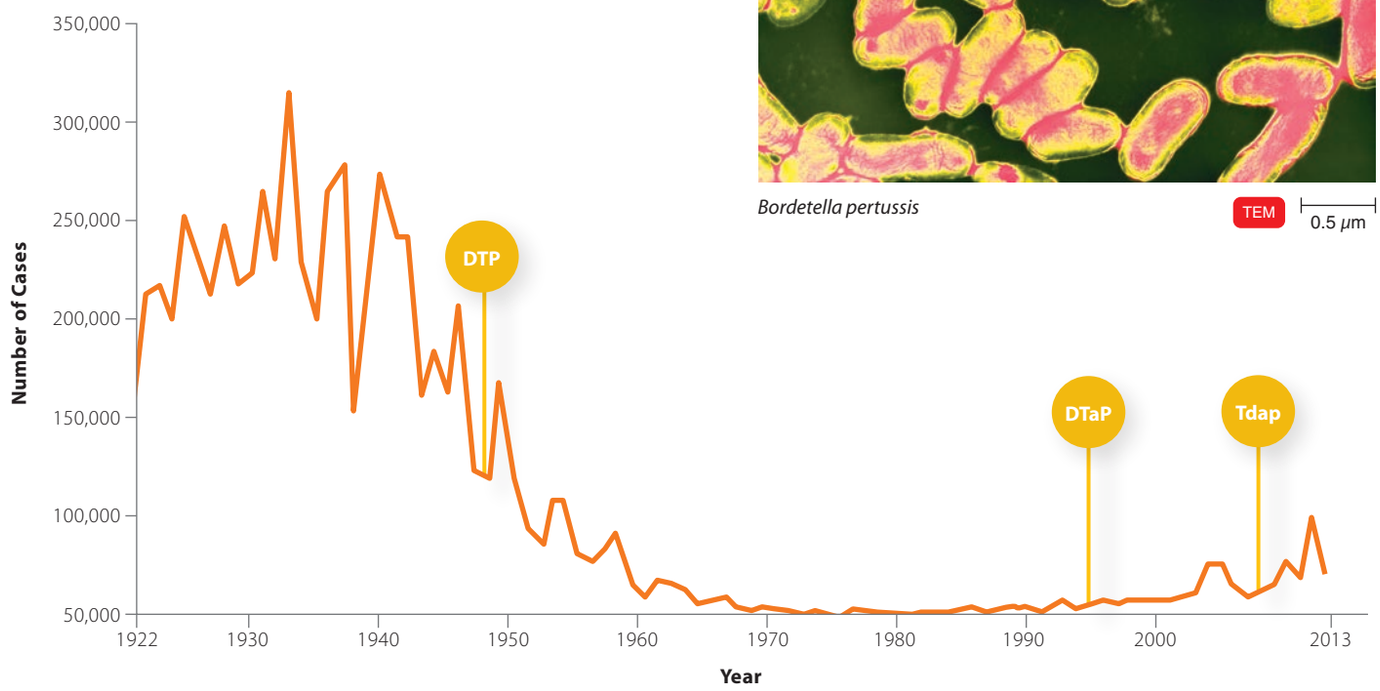
This fear, along with evidence that the DTP vaccine led to neurological conditions in some children, led U.S. health officials to pursue a safer pertussis vaccine. By 1997 DTP was completely phased out in the United States and replaced by the diphtheria, tetanus, acellular pertussis (DTaP) vaccine.

As the name implies, DTaP is an *acellular vaccine*. Since it doesn't contain whole pertussis cells, it is safer. Children routinely receive DTaP immunizations.





Bordetella pertussis TEM 0.5 μm



Reported Pertussis Cases in the U.S.: 1922–2013. *Source:* CDC.

New Booster Vaccinations Fight the Reemergence of Pertussis

Tracking Incidence and Hunting for Answers

After DTaP was phased in, health care providers began reporting pertussis cases to local health departments, statistics that feed into national reports issued by the CDC. Epidemiologists noted a trend of increased pertussis cases and began studying possible causes, including the following:

- A breakdown in herd immunity may have occurred. Part of the problem was a decline in the vaccination rate starting in the 1990s, when some parents avoided or delayed immunization because of misguided fears about links between autism and childhood vaccinations. However, decades of research have found no link between autism and immunization.
- *Bordetella pertussis* may have mutated in ways that made the vaccine less effective.
- The newer DTaP formulation may have been less effective than the old DTP formulation.
- Better diagnostic tests such as the polymerase chain reaction (PCR) may have led to more pertussis reporting without a corresponding increase in actual cases among the population.

Fast-Waning Immunity of DTaP Discovered

During the 2012 outbreak, researchers found that a significant number of people aged 13–14 contracted the disease. These teens had high childhood vaccination rates but were a few years past the last of their five DTaP doses. This group also happened to be among the first generation to receive only the acellular vaccine. Researchers began to suspect fast-waning immunity of DTaP. More research conducted by the Kaiser Permanente Vaccine Study Center supported the hypothesis that the acellular pertussis vaccine's long-term immunity was lower than expected.

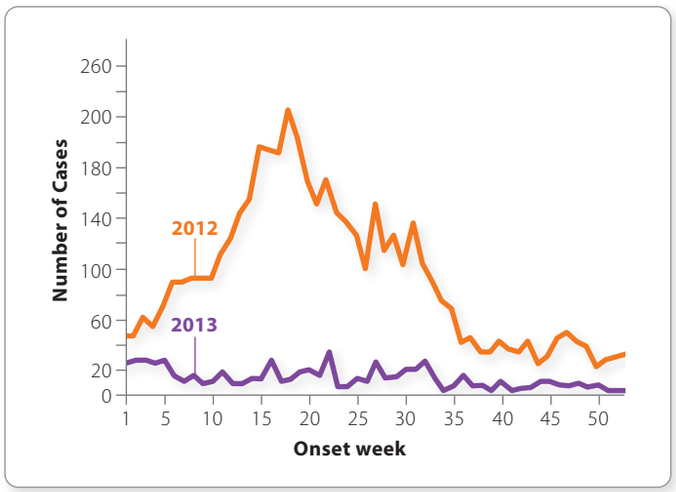
New Strategies for Fighting Pertussis

Once epidemiologists saw immunity fading among the adolescent population, they created a plan to lower incidence, which included the following:

- A new vaccine booster (a slightly different formulation from DTaP, called Tdap) was recommended for adolescents and adults.
- The CDC now recommends that pregnant women receive boosters to provide additional protection to newborns.
- Some regions implemented an additional pertussis booster vaccination requirement for public school attendance.
- Government health campaigns aimed at both patients and caregivers increased awareness of the epidemic, waning immunity, and the need for further immunizations.



CDC public health poster



Number of pertussis cases reported in Washington state by notication week, 2012 vs. 2013. Source: *Weekly Pertussis Update for Washington State,* October 5, 2013, Washington State Department of Health.

Are New Measures Working?

There is evidence that increases in booster rates are decreasing the disease's incidence. In Washington, one state hit hard by pertussis, vaccinations increased by 140% in 2012 compared to the year before the epidemic. As the graph above shows, by 2013 Washington's pertussis cases returned to near pre-epidemic levels.

KEY CONCEPTS

- Disease incidence tracking and other follow-up studies are key to identifying and addressing public health challenges. **(See Chapter 14, "Epidemiology," pages 407–412.)**
- Vaccinated people act as an important barrier to infection for individuals who are not immune. **(See Chapter 14, herd immunity, page 397.)**
- Depending, in part, on how they are made, vaccines have different risk factors and effects. **(See Chapter 18, "Types of Vaccines and Their Characteristics," pages 495–500.)** For pertussis, moving to a vaccine with fewer side effects has meant shorter-term immunity.

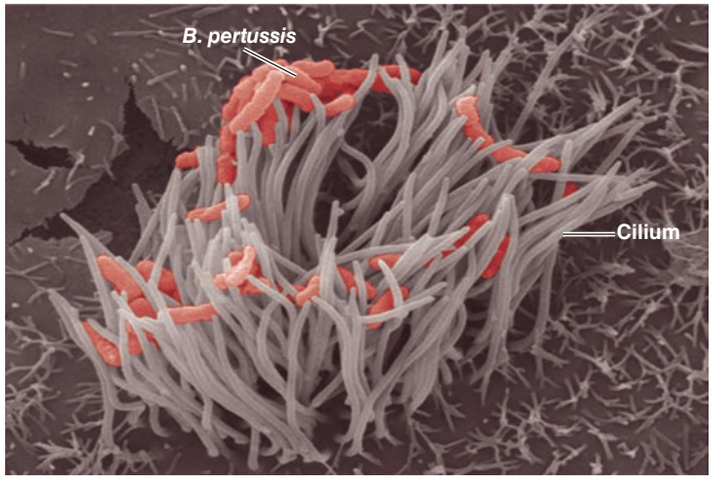


Figure 24.6 Ciliated cells of the respiratory system infected with *Bordetella pertussis*. Cells of *B. pertussis* (orange) can be seen growing on the cilia; they will eventually cause the loss of the ciliated cells.

What is the name of the toxin produced by *Bordetella pertussis* that causes the loss of cilia?

bacterium, is responsible for damage to the ciliated cells, and *pertussis toxin* enters the bloodstream and is associated with systemic symptoms of the disease.

Primarily a childhood disease, pertussis can be quite severe. The initial stage, called the *catarrhal stage,* resembles a common cold. Prolonged sieges of coughing characterize the *paroxysmal stage,* or second stage. (The name *pertussis* is derived from the Latin *per,* meaning thoroughly, and *tussis,* meaning cough.) When ciliary action is compromised, mucus accumulates, and the infected person desperately attempts to cough up these mucus accumulations. The violence of the coughing in small children can actually result in broken ribs. Gasping for air between coughs causes a whooping sound, hence the informal name of the disease. Coughing episodes occur several times a day for 1 to 6 weeks. The *convalescence stage,* the third stage, may last for months. Because infants are less capable of coping with the effort of coughing to maintain an airway, irreversible damage to the brain occasionally occurs.

Diagnosis of pertussis is primarily based on clinical signs and symptoms. The pathogen can be cultured from a throat swab inserted through the nose on a thin wire and held in the throat while the patient coughs. Culture of the fastidious pathogen requires care. As alternatives to culture, PCR methods can also be used to test the swabs for presence of the pathogen, a procedure that is required to diagnose the disease in infants.

Treatment of pertussis with antibiotics, most commonly erythromycin or other macrolides, is not effective after onset of the paroxysmal coughing stage but may reduce transmission.

CHECK YOUR UNDERSTANDING

Another name for pertussis is whooping cough. This symptom is caused by the pathogens' attack on which cells? **24-6**

Tuberculosis

In Europe during the seventeenth through the nineteenth centuries, **tuberculosis (TB)** was responsible for an estimated 20–30% of all deaths. This probably exerted a strong selection pressure for genes that protected against TB in this population. However, in recent decades co-infection with HIV has been a prominent cause of increasing susceptibility to infection and also of rapid progression from infection to active disease. Other factors are the increasing populations of susceptible individuals in prisons and other crowded facilities, as well as the elderly or undernourished.

Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculosis,* a slender rod and an obligate aerobe. The rods grow slowly (20-hour or longer generation time), sometimes form filaments, and tend to grow in clumps (**Figure 24.7**). On the surface of liquid media, their growth appears moldlike, which suggested the genus name *Mycobacterium* (*myco* means fungus).

Another mycobacterial species, *Mycobacterium bovis* (BŌ-vis), is a pathogen mainly of cattle. *M. bovis* is the cause of **bovine tuberculosis,** which is transmitted to humans via contaminated milk or food. Bovine tuberculosis accounts for fewer than 1% of TB cases in the United States. It seldom spreads from human to human, but before the days of pasteurized milk and the development of control methods such as tuberculin testing

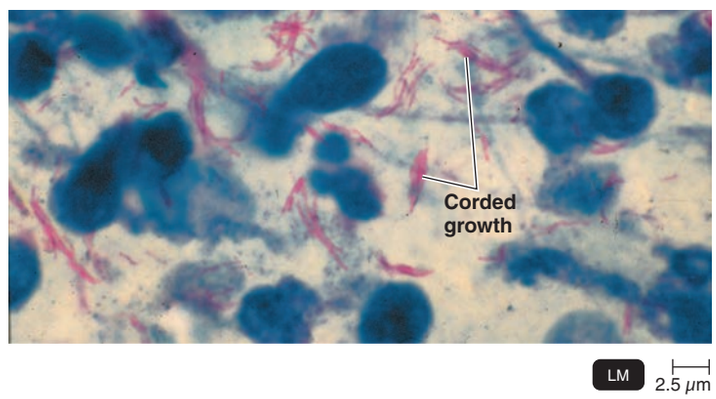


Figure 24.7 *Mycobacterium tuberculosis*. The filamentous, red-stained fungus-like growth shown here in a smear from lung tissue is responsible for the organism's name. Under other conditions, it grows as slender, individual bacilli. A waxy component of the cell, cord factor, is responsible for this ropelike arrangement. An injection of cord factor causes pathogenic effects exactly like that caused by tubercle bacilli.

What characteristic of this bacterium suggests use of the prefix *myco-*?

of cattle herds, this disease was a frequent form of tuberculosis in humans. *M. bovis* infections cause TB that primarily affects the bones or lymphatic system. At one time, a common manifestation of this type of TB was hunchbacked deformation of the spine.

Other mycobacterial diseases also affect people in the late stages of HIV infection. A majority of the isolates are of a related group of organisms known as the *M. avium-intracellulare* (Ā-vē-um in-TRAH-sel-ū-lar-ē) complex. In the general population, infections by these pathogens are uncommon.

Mycobacteria stained with carbol-fuchsin dye cannot be decolorized with acid-alcohol and are therefore classified as *acid-fast* (see page 66). This characteristic reflects the unusual composition of the cell wall, which contains large amounts of lipids. These lipids might also be responsible for the resistance of mycobacteria to environmental stresses, such as drying. In fact, these bacteria can survive for weeks in dried sputum and are very resistant to chemical antimicrobials used as antiseptics and disinfectants (see Table 7.7 page 195).

Tuberculosis is a particularly good illustration of the ecological balance between host and parasite in infectious disease. A host is not usually aware of tuberculosis pathogens that invade the body and are defeated, which occurs 90% of the time. If immune defenses fail, however, the host becomes very much aware of the resulting disease.

A tragic demonstration of individual variation in resistance was the Lübeck disaster in Germany in 1926. By error, 249 babies were inoculated with virulent tuberculosis bacteria instead of the attenuated vaccine strain. Even though all received the same inoculum, there were only 76 deaths, and the remainder did not become seriously ill.

Tuberculosis is most commonly acquired by inhaling the bacillus. Only very fine particles containing one to three bacilli reach the lungs, where they are usually phagocytized by a macrophage in the alveoli (see Figure 24.2). The macrophages of a healthy individual become activated by the presence of the bacilli and usually destroy them. About three-fourths of TB cases affect the lungs, but other organs can also become infected.

Pathogenesis of Tuberculosis

The pathogenesis of TB is shown in **Figure 24.8**. An important factor in the pathogenicity of the mycobacteria probably is that the mycolic acids of the cell wall strongly stimulate an inflammatory response in the host. The figure depicts the situation in which the body's defenses fail and the disease progresses to a fatal conclusion. However, most healthy people will defeat a potential infection with activated macrophages, especially if the infecting dose is low.

1–2 If the infection progresses, the host isolates the pathogens in a walled-off lesion called a *tubercle* (meaning lump or knob), a characteristic that gives the disease its name.

3–4 When the disease is arrested at this point, the lesions slowly heal, becoming calcified. These show up clearly on X-ray films and are called *Ghon's complexes.* (Computed tomography [CT] is more sensitive than X rays in detecting lesions of TB.)

5 If the body's defenses fail at this stage, the tubercle breaks down and releases virulent bacilli into the airways of the lung and then the cardiovascular and lymphatic systems.

Coughing, the more obvious symptom of the lung infection, also spreads the infection by bacterial aerosols. Sputum may become bloodstained as tissues are damaged, and eventually blood vessels may become so eroded that they rupture, resulting in fatal hemorrhaging. The disseminated infection is called *miliary tuberculosis* (the name is derived from the numerous millet seed–sized tubercles formed in the infected tissues). The body's remaining defenses are overwhelmed, and the patient suffers weight loss and a general loss of vigor. At one time, TB was also known as *consumption.*

Diagnosis of Tuberculosis

People infected with tuberculosis respond with cell-mediated immunity against the bacterium. This form of immune response, rather than humoral immunity, develops because the pathogen is located mostly within macrophages. This immunity, involving sensitized T cells, is the basis for the **tuberculin skin test** (**Figure 24.9**), a screening test for infection. A positive test does not necessarily indicate active disease. In this test, a purified protein derivative of the tuberculosis bacterium, derived by precipitation from broth cultures, is injected cutaneously. If the injected person has been infected with TB in the past, sensitized T cells react with these proteins, and a delayed hypersensitivity reaction occurs in about 48 hours. This reaction appears as an induration (hardening) and reddening of the area around the injection site. Probably the most accurate tuberculin test is the *Mantoux test,* in which dilutions of 0.1 ml of antigen are injected and the reacting area of the skin is measured.

A positive tuberculin test in the very young is a probable indication of an active case of TB. In older individuals, it might indicate only hypersensitivity resulting from a previous infection or vaccination, not a current active case. Nonetheless, it is an indication that further examination is needed, such as a chest X-ray or CT examination to detect lung lesions and attempts to isolate the bacterium.

The initial step in laboratory diagnosis of active cases is a microscopic examination of smears, such as sputum. According to recent medical opinion, the commonly used 125-year-old microscopic exam routinely misses half of all cases. Confirming a diagnosis of TB by isolating the bacterium poses difficulties because the pathogen grows very slowly. A colony might take 3 to 6 weeks to form, and completing a reliable identification series may add another 3 to 6 weeks.

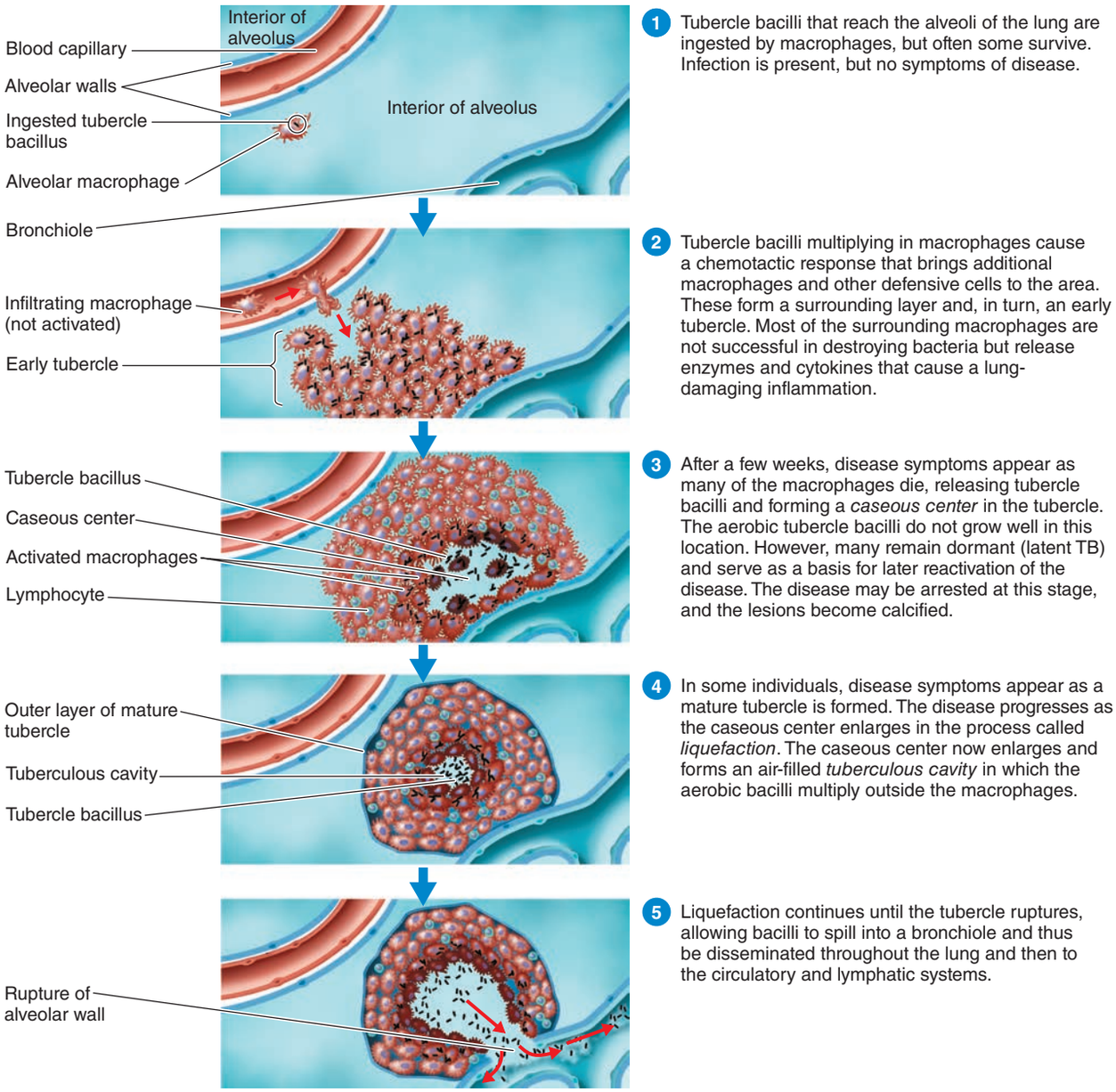


Figure 24.8 The pathogenesis of tuberculosis. This figure represents the progression of the disease when the defenses of the body fail. In most otherwise healthy individuals, the infection is arrested, and fatal tuberculosis does not develop.

Q Almost a third of Earth's population is infected with *Mycobacterium tuberculosis*—does a study of this figure show why this is not the same as a third of Earth's population *having* tuberculosis?

In recent years there has been progress in developing rapid diagnostic tests, at least in more affluent countries. These blood tests, QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-SPOT TB test (T-Spot), measure a person's IFN-γ. They are the preferred tests for a person who has received BCG vaccinations.

A new automated PCR test (Xpert MTB/RIF) can diagnose TB by detecting *M. tuberculosis* within 90 minutes. At the same time it determines resistance to a major TB antibiotic, rifampin. It can be used by relatively unskilled workers, but a disadvantage is its high cost.

Evidence indicates that, compared to the skin test, these rapid tests have higher specificity and less cross-reactivity with BCG vaccination (see the discussion of TB vaccines, following). They do not distinguish latent from active infection. These assays seem likely to replace the tuberculin skin test for many uses, especially where cross-reactivity with BCG vaccination is

a problem. If they could be adopted worldwide at centers for TB treatment, they would help avert millions of TB-related deaths.

Treatment of Tuberculosis

The first effective antibiotic for TB treatment was streptomycin, which was introduced in 1944. Streptomycin is still in use, and all of the currently used drugs were developed decades ago. Even the *short course* of treatment for TB (there are variations in the regimen, depending on sensitivity of the organism and other factors) requires the patient to adhere to a minimum of 6 months of therapy. Multiple-drug therapy is needed to minimize the emergence of resistant strains. This typically includes four drugs, isoniazid, ethambutol, pyrazinamide, and rifampin, which are considered **first-line drugs.** If the strain of *M. tuberculosis* is susceptible to the drugs, this regimen can lead to a cure. The likelihood that resistance may develop is increased because many patients fail to faithfully follow such a prolonged regimen, which can involve 130 doses of the drugs.

In addition to the first-line drugs, there are a number of **second-line drugs** that can be used, mainly if resistance develops to alternatives. These include several aminoglycosides, fluoroquinolones, and para-aminosalicylic acid (PAS). These drugs are either less effective than first-line drugs, have toxic side effects, or may be unavailable in some countries.

The prolonged treatment is necessary because the tubercle bacillus grows very slowly or is only dormant (the only drug effective against the dormant bacillus is pyrazinamide), and many antibiotics are effective only against growing cells. Also, the bacillus may be hidden for long periods in macrophages or other locations that are difficult to reach with antibiotics.

Not surprisingly, problems have arisen with cases of TB that are caused by **multi-drug-resistant (MDR)** strains. These are defined as being resistant to the two most effective first-line drugs, isoniazid and rifampin. In addition, strains have arisen that are also resistant to the most effective second-line drugs, such as any fluoroquinolone, and to at least one of three injectable second-line drugs, such as the aminoglycosides *amikacin* or *kanamycin,* as well as the polypeptide *capreomycin*. These cases, defined as **extensively drug-resistant (XDR),** are virtually untreatable and are emerging globally. An additional consideration is that anywhere from 30–90% of persons with TB are also HIV positive—with the accompanying damage to the immune system. In one study, all patients testing positive for both HIV and XDR tuberculosis died within 3 months of diagnosis.

Obviously, there is a pressing need for new, effective drugs to treat TB, especially XDR cases. In 2012, bedaquiline was approved to treat MDR TB in adults.

Testing for Drug Susceptibility

The current culture-based methods for drug-susceptibility testing, which is considered the so-called gold standard, can take as long as 4 to 8 weeks for finalized results. Certain newly developed assays take advantage of the fact that the pathogen grows faster in liquid media. These assays are simultaneously useful for both diagnosis and determination of drug susceptibility. The Microscopic-Observation Drug-Susceptibility Assay (MODS) is based on direct observation of the typical cording growth (see Figure 24.7) of *M. tuberculosis* in liquid cultures, requires only 6 to 8 days, and is relatively inexpensive. The determination of susceptibility for rifampin is about 100% and can be considered a marker for potential resistance to other drugs. Recall that the Xpert MTB/RIF diagnostic assay also rapidly tests for rifampin resistance. Another assay, Hain Genotype MTBDRplus, is a reliable, rapid, and relatively inexpensive diagnostic test that can also be used for detecting drug-resistant strains. It is a PCR assay that can even be used on sputum samples. Within 1 or 2 days it can diagnostically detect *M. tuberculosis* and can measure resistance to rifampin and isoniazid, as well.

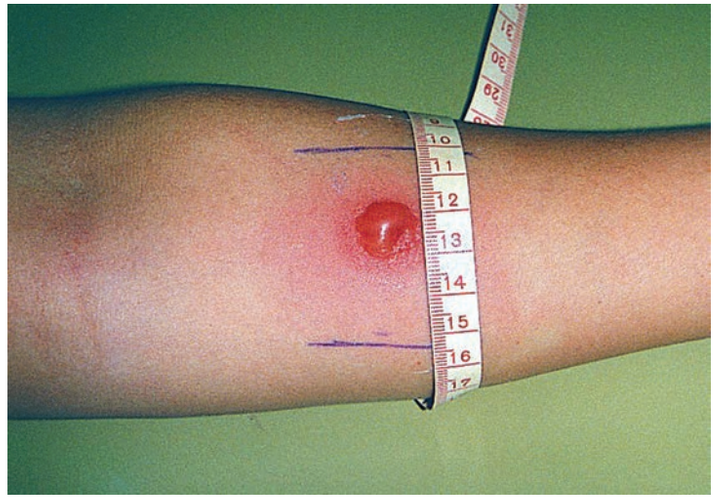
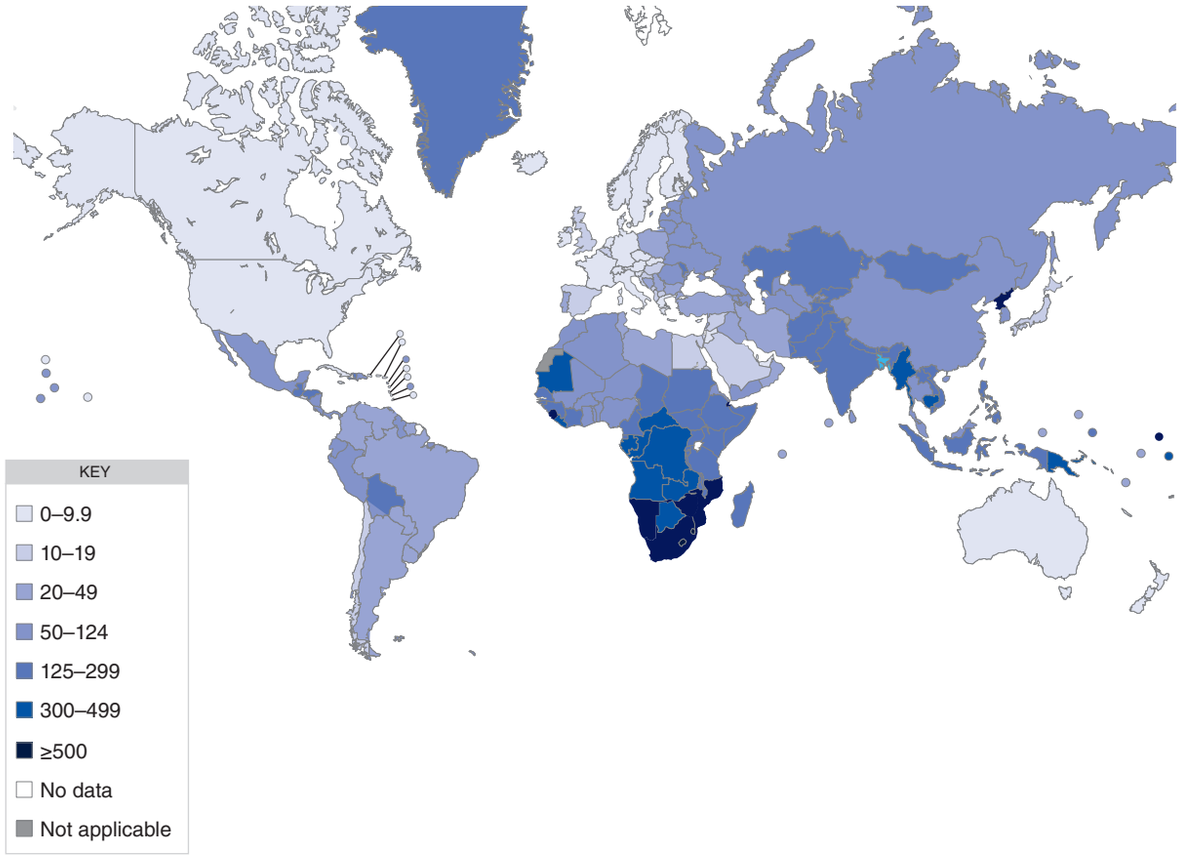


Figure 24.9 A positive tuberculin skin test on an arm.

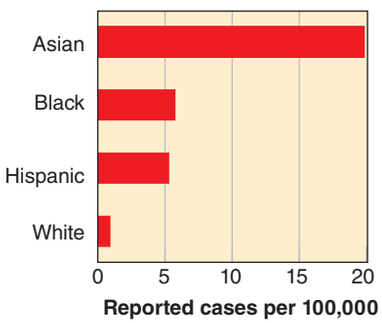
Q What does a positive tuberculin skin test indicate?

Tuberculosis Vaccines

The **BCG vaccine** is a live culture of *M. bovis* that has been made avirulent by long cultivation on artificial media. (BCG stands for bacillus of Calmette and Guérin, the French scientists who originally isolated the strain.) The BCG vaccine has been available since the 1920s and is one of the most widely used vaccines in the world. In 1990, it was estimated that 70% of the world's schoolchildren received it. In the United States, however, the vaccine is currently recommended only for certain children at high risk who have negative skin tests. People who have received the vaccine show a positive reaction to tuberculin skin tests. This has always been one argument against its widespread use in the United States. Another argument against the universal administration of BCG vaccine is its very uneven effectiveness. Experience has shown that it is fairly effective when given to



(a) Estimated tuberculosis incidence worldwide, per 100,000 population



(b) Reported tuberculosis cases per 100,000 population among American ethnic groups in 2012

Figure 24.10 Distribution of tuberculosis. **(a)** Tuberculosis worldwide. **(b)** Tuberculosis in the United States. Rates among American ethnic groups.

Source: World Health Organization (WHO), 2014; *MMWR* 62(11): 201–205, March 22, 2013

How can tuberculosis be eliminated?

young children, but for adolescents and adults it sometimes has an effectiveness approaching zero. Worse, it has been found that HIV-infected children, who need it most, frequently will develop a fatal infection from the BCG vaccine. Recent work indicates that exposure to members of the *M. avium-intracellulare* complex that is often encountered in the environment may interfere with the effectiveness of the BCG vaccine—which might explain why the vaccine is more effective early in life, before much exposure to such environmental mycobacteria. A number of new vaccines are in the experimental pipeline, but they will require large numbers of human samples and several years of follow-up to evaluate.

Worldwide Incidence of Tuberculosis

Tuberculosis has emerged as a global pandemic (Figure 24.10a). Estimates are that 9 million people develop active tuberculosis

every year and that infections result in more than 2 million deaths annually. (Worldwide, the incidence of TB per capita is falling at about 1% a year. However, the world population is growing at about 2% a year—therefore, the total number of new TB cases is still rising.) Probably a third of the world's population is infected. Also, HIV and tuberculosis are almost inseparable, and tuberculosis is the leading direct cause of death in much of the world affected by HIV. The majority of TB cases in the United States, usually around 10,000 annually, occur among foreign-born individuals who are infected in their countries of origin (Figure 24.10b).

Bacterial Pneumonias

The term *pneumonia* is applied to many pulmonary infections, most of which are caused by bacteria. Pneumonia caused by *Streptococcus pneumoniae* is the most common, about two-thirds of cases, and is therefore referred to as *typical pneumonia.* Pneumonias caused by other microorganisms, which can include fungi, protozoa, viruses, and other bacteria, especially mycoplasma, are termed *atypical pneumonias.* This distinction is becoming increasingly blurred in practice.

Pneumonias also are named after the portions of the lower respiratory tract they affect. For example, if the lobes of the lungs are infected, it is called *lobar pneumonia;* pneumonias caused by *S. pneumoniae* are usually of this type. *Bronchopneumonia* indicates that the alveoli of the lungs adjacent to the bronchi are infected. *Pleurisy* is often a complication of various pneumonias, in which the pleural membranes become painfully inflamed. (See Diseases in Focus 24.2.)

Pneumococcal Pneumonia

Pneumonia caused by *S. pneumoniae* is called **pneumococcal pneumonia.** *S. pneumoniae* is a gram-positive, ovoid bacterium (**Figure 24.11**). This microbe is also a common cause of otitis media, meningitis, and sepsis. The cell pairs are surrounded by a dense capsule that makes the pathogen resistant to phagocytosis. These capsules are also the basis of serological differentiation of pneumococci into at least 90 serotypes. Most human infections are caused by only 23 variants, and these are the basis of current vaccines. Before antibiotic therapy became available, antisera directed at these capsular antigens were used to treat the disease.

Pneumococcal pneumonia involves both the bronchi and the alveoli (see Figure 24.2). Symptoms include high fever, breathing difficulty, and chest pain. (Atypical pneumonias usually have a slower onset and less fever and chest pain.) The lungs have a reddish appearance because blood vessels are dilated. In response to the infection, alveoli fill with some red blood cells, neutrophils (see Table 16.1, page 447), and fluid from surrounding tissues. The sputum is often rust-colored from blood coughed up from the lungs. Pneumococci can invade the bloodstream, the pleural cavity surrounding the lung, and occasionally the meninges. No bacterial toxin has been clearly related to pathogenicity.

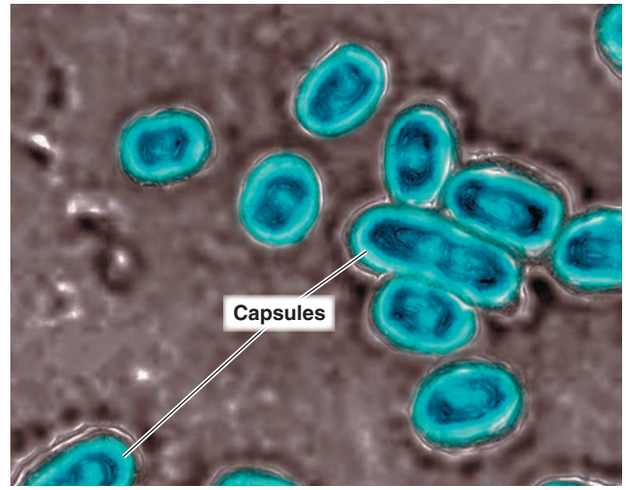


Figure 24.11 ***Streptococcus pneumoniae,*** **the cause of pneumococcal pneumonia.** Some of the cocci in the photo are undergoing division and appear as extended ovals. The prominent capsule refracts light and appears as a bright outline.

Q What component of the cell is the primary antigen?

A presumptive diagnosis can be made by isolating the pneumococci from the throat, sputum, and other fluids. Pneumococci can be distinguished from other alpha-hemolytic streptococci by observing the inhibition of growth next to a disk of optochin (ethylhydrocupreine hydrochloride) or by performing a bile solubility test. A new test that detects a specific antigen of *S. pneumoniae* in the urine can be performed in a physician's office and, with 93% accuracy, can make a diagnosis in 15 minutes.

There are many healthy carriers of the pneumococcus. Virulence of the bacteria seems to be based mainly on the carrier's resistance, which can be lowered by stress. Many illnesses of older adults terminate in pneumococcal pneumonia.

A recurrence of pneumococcal pneumonia is not uncommon, but the serological types are usually different. Before chemotherapy was available, the mortality rate was as high as 25%. This has now been lowered to less than 1% for younger patients treated early in the course of their disease. For older patients admitted to a hospital, mortality can approach 20%.

Resistance to penicillin has been an increasing problem, and several other drugs, especially macrolides and fluoroquinolones, are now replacing it.

A conjugated pneumococcal vaccine has recently been introduced that has been effective in preventing infection by the seven serotypes included in it. It has also had an indirect herd effect shown by reduction in other diseases, such as otitis media, attributable to the pneumococcus.



Figure 24.12 Colonies of *Mycoplasma pneumoniae,* the cause of mycoplasmal pneumonia.

Could you see these colonies without magnification?

Haemophilus influenzae Pneumonia

Haemophilus influenzae is a gram-negative coccobacillus, and a Gram stain of sputum will differentiate this type of pneumonia from pneumococcal pneumonia. Patients with such conditions as alcoholism, poor nutrition, cancer, or diabetes are especially susceptible. Diagnostic identification of the pathogen uses special media that determine requirements for X and V factors (see page 301). Second-generation cephalosporins are resistant to the β-lactamases produced by many *H. influenzae* strains and are therefore usually the drugs of choice.

Mycoplasmal Pneumonia

The mycoplasmas, which do not have cell walls, do not grow under the conditions normally used to recover most bacterial pathogens. Because of this characteristic, pneumonias caused by mycoplasmas are often confused with viral pneumonias.

The bacterium *Mycoplasma pneumoniae* is the causative agent of **mycoplasmal pneumonia.** This type of pneumonia was first discovered when such atypical infections responded to tetracyclines, indicating that the pathogen was nonviral. Mycoplasmal pneumonia is a common type of pneumonia in young adults and children. It may account for as much as 20% of pneumonias, although it is not a reportable disease. The symptoms, which persist for 3 weeks or longer, are low-grade fever, cough, and headache. Occasionally, they are severe enough to lead to hospitalization. Other terms for the disease are *primary atypical* (that is, the most common pneumonia not caused by the pneumococcus) and *walking pneumonia.*

When isolates from throat swabs and sputum grow on a medium containing horse serum and yeast extract, some form distinctive colonies with a "fried-egg" appearance (Figure 24.12). The colonies are so small that they must be observed with magnification. The mycoplasmas are highly varied in appearance because they lack cell walls (see Figure 11.24, page 311).

Diagnosis based on recovering the pathogens might not be useful in treatment because as long as 3 or more weeks may be required for the slow-growing organisms to develop. Diagnostic tests have improved greatly in recent years, however. They include PCR and serological tests that detect IgM antibodies against *M. pneumoniae.*

Treatment with antibiotics such as tetracycline usually hastens the disappearance of symptoms but does not eliminate the bacteria, which the patient continues to carry for several weeks.

Legionellosis

Legionellosis, or **Legionnaires' disease,** first received public attention in 1976, when a series of deaths occurred among members of the American Legion who had attended a meeting in Philadelphia. Because no obvious bacterial cause could be found, the deaths were attributed to viral pneumonia. Close investigation, mostly with techniques directed at locating a suspected rickettsial agent, eventually identified a previously unknown bacterium, an aerobic gram-negative rod now known as *Legionella pneumophila,* which is capable of replication within macrophages. Over 44 species of *Legionella* have now been identified; not all of them cause disease.

The disease is characterized by a high fever of 40.5°C, cough, and general symptoms of pneumonia. No person-to-person transmission seems to be involved. Recent studies have shown that the bacterium can be readily isolated from natural waters. In addition, the microbes can grow in the water of air-conditioning cooling towers, perhaps indicating that some epidemics in hotels, urban business districts, and hospitals were caused by airborne transmission. Recent outbreaks have been traced to whirlpool spas, humidifiers, showers, decorative fountains, and even potting soil.

The organism has also been found to inhabit the water lines of many hospitals. Most hospitals keep the temperature of hot water lines relatively low (43–55°C) as a safety measure, and in cooler parts of the system this inadvertently maintains a good growth temperature for *Legionella.* This bacterium is considerably more resistant to chlorine than most other bacteria and can survive for long periods in water with a low level of chlorine. Evidence indicates *Legionella* exist primarily in biofilms that are highly protective. The bacteria are often ingested by waterborne amoebae when these are present but continue to proliferate and may even survive within encysted amoebae. The most successful method for water disinfection in hospitals with a need to control *Legionella* contamination has been installation of copper-silver ionization systems.

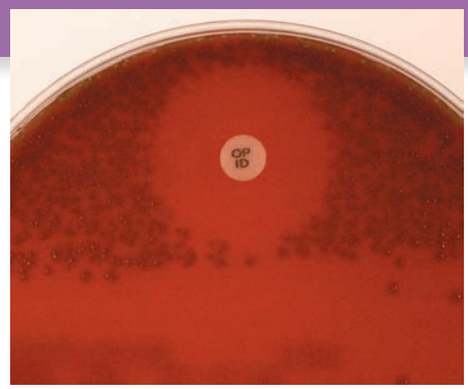
The disease appears to have always been fairly common, if unrecognized. More than 1000 cases are reported each year, but the actual incidence is estimated at over 25,000 annually. Men over 50 are the most likely to contract legionellosis, especially heavy smokers, alcohol abusers, or the chronically ill. (See the Clinical Focus box on page 694.)

DISEASES IN FOCUS 24.2

Common Bacterial Pneumonias

Pneumonia is a leading cause of illness and death among children worldwide and the seventh leading case of death in the United States. Pneumonia can be caused by a variety of viruses, bacteria, and fungi. To prove that a bacterium is causing the pneumonia, the bacterium is isolated from cultures of blood or, in some cases, lung aspirates.

A 27-year-old man with a history of asthma is hospitalized with a 4-day history of progressive cough and 2 days of spiking fevers. Gram-positive cocci in pairs are cultured from a blood sample. Use the table below to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



An optochin-inhibition test of the cultured bacteria, on blood agar.

Disease	Pathogen	Symptoms	Reservoir	Diagnosis	Treatment
Pneumococcal Pneumonia	*Streptococcus pneumoniae*	Infected alveoli of lung fill with fluids; interferes with oxygen uptake	Humans	Positive optochin inhibition test or bile solubility test; serological typing of bacteria	Fluoroquinolones Prevention: pneumococcal vaccine
***Haemophilus influenzae* Pneumonia**	*Haemophilus influenzae*	Symptoms resemble pneumococcal pneumonia	Humans	Isolation; special media for nutritional requirements	Cephalosporins
Mycoplasmal Pneumonia	*Mycoplasma pneumoniae*	Mild but persistent respiratory symptoms; low fever, cough, headache	Humans	PCR and serological tests	Tetracyclines
Legionellosis	*Legionella pneumophila*	Potentially fatal pneumonia	Water	Culture on selective media; DNA probe	Erythromycin
Psittacosis (Ornithosis)	*Chlamydophila psittaci*	Symptoms, if any, are fever, headache, chills	Birds	Growth of bacteria in eggs or cell culture	Tetracyclines
Chlamydial Pneumonia	*Chlamydophila pneumoniae*	Mild respiratory illness; resembles mycoplasmal pneumonia	Humans	Serological tests	Tetracyclines
Q Fever	*Coxiella burnetii*	Mild respiratory disease lasting 1–2 weeks; occasional complications such as endocarditis occur	Large mammals; can be transmitted via unpasteurized milk	Growth in cell culture	Doxycycline and chloroquine

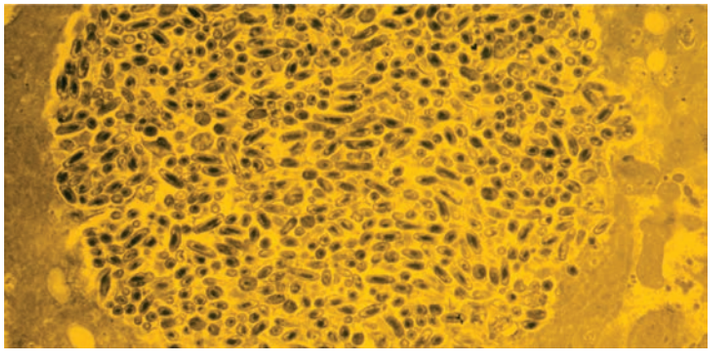
L. pneumophila is also responsible for **Pontiac fever,** which is essentially another form of legionellosis. Its symptoms include fever, muscular aches, and usually a cough. The condition is mild and self-limiting. During outbreaks of legionellosis, both forms may occur.

The best diagnostic method is culture on a selective charcoal–yeast extract medium. Respiratory specimens can be examined by fluorescent-antibody methods, and a DNA probe test is available. Erythromycin and other macrolide antibiotics, such as azithromycin, are the drugs of choice for treatment.

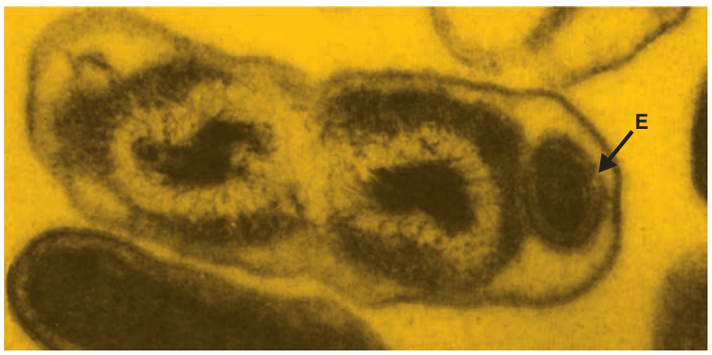
Psittacosis (Ornithosis)

The term **psittacosis** is derived from the disease's association with psittacine birds, such as parakeets and other parrots. It was later found that the disease can also be contracted from many other birds, such as pigeons, chickens, ducks, and turkeys. Therefore, the more general term **ornithosis** has come into use.

The causative agent is *Chlamydophila psittaci* (SIT-tah-sē), a gram-negative, obligate intracellular bacterium. The taxonomy of this organism has recently been revised. The genus name has been changed from *Chlamydia* to *Chlamydophila.* This taxonomic change has also been made with *C. pneumoniae* (see the discussion of chlamydial pneumonia that follows). We will continue to use the generic terms *chlamydial* and *chlamydiae.* One way chlamydiae differ from rickettsias, which are also obligate intracellular bacteria, is that chlamydiae form tiny **elementary bodies** as one part of their life cycle (see Figure 11.15, page 305). Unlike most rickettsias, elementary bodies are resistant to environmental stress; therefore, they can be transmitted through air and do not require a bite to transfer the infective agent directly from one host to another.



(a) Masses of *Coxiella burnetii* growing in a placental cell TEM 2 μm



(b) This cell has just divided; notice the endospore-like body (E), which is probably responsible for the relative resistance of the organism. TEM 0.5 μm

Figure 24.13 ***Coxiella burnetii,*** **the cause of Q fever.**

Q By what two methods is Q fever transmitted?

Psittacosis is a form of pneumonia that usually causes fever, coughing, headache, and chills. Subclinical infections are very common, and stress appears to enhance susceptibility to the disease. Disorientation, or even delirium in some cases, indicates that the nervous system can be involved.

The disease is seldom transmitted from one human to another but is usually spread by contact with the droppings and other exudates of fowl. One of the most common modes of transmission is inhalation of dried particles from droppings. The birds themselves usually have diarrhea, ruffled feathers, respiratory illness, and a generally droopy appearance. Parakeets and other parrots sold commercially are usually (but not always) free of the disease. Many birds carry the pathogen in their spleen without symptoms, becoming ill only when stressed. Pet store employees and people involved in raising turkeys are at greatest risk of contracting the disease.

Diagnosis is made by isolating the bacterium in embryonated eggs or by cell culture. Serological tests can be used to identify the isolated organism. No vaccine is available, but tetracyclines are effective antibiotics in treating humans and animals. Effective immunity does not result from recovery, even when high titers of antibody are present in the serum.

Most years, fewer than 100 cases and very few deaths are reported in the United States. The main danger is late diagnosis. Before antibiotic therapy was available, the mortality rate was about 15%–20%.

Chlamydial Pneumonia

Outbreaks of a respiratory illness in populations of college students were found to be caused by a chlamydial organism. Originally the pathogen was considered a strain of *C. psittaci,* but it has been assigned the species name *Chlamydophila pneumoniae,* and the disease is known as **chlamydial pneumonia.** Clinically, it resembles mycoplasmal pneumonia. (There is also strong evidence of association between *C. pneumoniae* and atherosclerosis, the deposition of fatty deposits that block arteries.)

The disease is apparently transmitted from person to person, probably by the respiratory route. Nearly half the U.S. population has antibodies against the organism, an indication that this is a common illness. Several serological tests are useful in diagnosis, but results are complicated by antigenic variation. The most effective antibiotic is tetracycline.

Q Fever

In Australia during the mid-1930s, a previously unreported flu-like pneumonia made an appearance. In the absence of an obvious cause, the affliction was labeled **Q fever** (for *query*), much as one might say "X fever." The causative agent was subsequently identified as the obligately parasitic, intracellular bacterium *Coxiella burnetii* (KOKS-ē-el-lah ber-NE-tē-ē) (**Figure 24.13a**). Currently, it is classified as a member of the gammaproteobacteria. Along with other bacteria of this group (such as the genera *Franciscella* and *Legionella*), it has the ability to multiply intracellularly. Most intracellular bacteria, such as rickettsia, are

Clinical Case

When the family's symptoms worsen, Caille makes appointments with Dr. Cantwell, the family physician. Because of the family's respiratory symptoms, Dr. Cantwell orders chest X-ray exams, which confirm lobar pneumonia in Caille, Art, and Steven. While in the doctor's office, the children tell Dr. Cantwell about Bitsy and how much they miss their pet cockatiel. Dr. Cantwell, recognizing that cockatiels are psittacine birds, takes a blood sample for antibody testing, prescribes tetracycline, and asks everyone to return in 1 month for convalescent serum samples.

Why does Dr. Cantwell want the sera tested?

not resistant enough to survive airborne transmission, but this microorganism is an exception.

Q fever has a wide range of clinical symptoms, and systematic testing shows that about 60% of cases are not even symptomatic. Cases of *acute Q fever* usually feature symptoms of high fever, headaches, muscle aches, and coughing. A feeling of malaise may persist for months. The heart becomes involved in about 2% of acutely ill patients and is responsible for the rare fatalities. In cases of *chronic Q fever,* the best known manifestation is endocarditis (see page 641). Some 5 to 10 years might elapse between the initial infection and the appearance of endocarditis; and, because these patients show few signs of acute disease, the association with Q fever is often missed. Antibiotic therapy and earlier diagnosis have lowered the mortality rate from chronic Q fever to under 5%.

C. burnetii is a parasite of several arthropods, especially cattle ticks, and it is transmitted among animals by tick bites. Infected animals include cattle, goats, and sheep, as well as most domestic mammalian pets. In animals the infection is usually subclinical. Cattle ticks spread the disease among dairy herds, and the microbes are shed in the feces, milk, and urine of infected cattle. Once the disease is established in a herd, it is maintained by aerosol transmission. The disease is spread to humans by ingesting unpasteurized milk and by inhaling aerosols of microbes generated in dairy barns, especially at calving time from placental material, which contains about a billion bacteria per gram.

Inhaling a single pathogen is enough to cause infection, and many dairy workers have acquired at least subclinical infections. Workers in meat- and hide-processing plants are also at risk. The pasteurization temperature of milk, which was originally aimed at eliminating tuberculosis bacilli, was raised slightly in 1956 to ensure the killing of *C. burnetii.* In 1981, an endospore-like body was discovered, which may account for this heat resistance (Figure 24.13b). This resistant body resembles the elementary body of chlamydiae more than typical bacterial endospores.

The pathogen can be identified by isolation and growth in chick embryos in eggs or in cell culture. Laboratory workers testing for *Coxiella*-specific antibodies in a patient's serum can use serological tests.

A disease found worldwide, most cases of Q fever in the United States occur in the western states. The disease is endemic to California, Arizona, Oregon, and Washington. A vaccine for laboratory workers and other high-risk personnel is available. Doxycycline has been recommended for treatment. When growth within macrophages in chronic infections renders *C. burnetii* resistant, the killing activity can be restored by combining doxycycline with chloroquine, an antimalarial. The chloroquine raises the pH of the phagosome, increasing doxycycline's efficiency.

Melioidosis

In 1911, a new disease was reported among drug addicts in Rangoon, Burma (now Myanmar). The bacterial pathogen, *Burkholderia pseudomallei,* is a gram-negative rod formerly placed in the genus *Pseudomonas.* It closely resembled the bacterium causing glanders, a disease of horses. Therefore, the disease was named **melioidosis** (mel-ē-oi-DŌ-sis) from the Greek *melis* (distemper of asses) and *eidos* (resemblance). It is now recognized as a major infectious disease in southeast Asia and northern Australia, where the pathogen is widely distributed in moist soils. It most commonly affects individuals with lower immune capabilities—frequently diabetics. Sporadic cases are reported in Africa, the Caribbean, Central and South America, and the Middle East. Many animal species are also susceptible.

Clinically, melioidosis is most commonly seen as pneumonia. Mortality arises from dissemination, manifesting itself as septic shock. The mortality rate in southeast Asia is about 50% and in Australia approaches 20%. However, it can also appear as abscesses in various body tissues that resemble necrotizing fasciitis (see Figure 21.8, page 585), as severe sepsis, and even as encephalitis. Transmission is primarily by inhalation, but alternative infective routes are by inoculation through puncture wounds and ingestion. About 7% of American soldiers returning from Vietnam showed serological evidence of exposure, which was highest among helicopter crewmen—probably from inhalation. Incubation periods can be very long, and occasional delayed-onset cases still surface in this population. There have been outbreaks of melioidosis in Asia in recent years. A cluster of cases in a remote village in western Australia occurred following an earthquake, and in Taiwan a limited outbreak was reported in the aftermath of the damaging typhoon of 2005.

Clinical Case

Dr. Cantwell suspects psittacosis because of the evidence of respiratory disease and recent exposure to a cockatiel. The Nguyens are all feeling better when they return to provide convalescent serum the following month. Indirect FA test results of their sera are shown below.

	Titer against *Chlamydophila psittaci*	
Nguyen Family Member	**Acute Serum**	**Convalescent Serum**
Caille	0	0
Art	32	16
Gabbie	64	32
Steven	64	32
Tre	128	64

What do these data indicate?

CLINICAL FOCUS

Outbreak

As you read through this problem, you will see questions that epidemiologists ask themselves and each other as they solve a clinical problem. Try to answer each question as though you were an epidemiologist.

1. Jerry Roberts, a 64-year-old man, sees his primary care physician, complaining of fever, malaise, and a cough. His vaccinations are up-to-date, including DTaP. His condition worsens over several days; he has difficulty breathing, and his temperature rises to 40.4°C. He is hospitalized, and his lungs show signs of mild inflammation with thin, watery secretion. A Gram stain of bacteria isolated from the patient is shown in the photo.

   What diseases are possible?

2. The same day, Antonio Viviano, a 37-year-old man, goes to the emergency department because he has shortness of breath, fatigue, and cough. The day before he had fever and chills, with a maximum body temperature of 38.6°C.

   What additional tests would you do on both patients?

3. PCR, lab cultures, and serological tests should be run on both patients. Both patients have an antibody titer >1024 against *Legionella pneumophila* serogroup 1. The local health department is contacted because two patients are hospitalized with legionellosis.

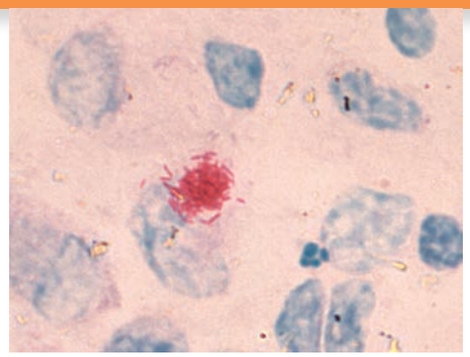
   What do you need to know now?

4. Both patients should be asked whether they have traveled recently, and if so, where. One week before hospitalization, both men stayed in the same hotel within one day of each other. Six additional cases of legionellosis were identified at other hospitals. A follow-up questionnaire is given to all eight patients to ascertain travel that preceded the illness, including location, accommodations, dates, and information about exposures to common sources for infection (see the table).

   What are likely sources of infection?

5. Epidemic legionellosis usually results from exposure of susceptible individuals to an aerosol generated by an environmental source of water contaminated with *Legionella*.

Patient's Travel History	
Age	37–70 yrs (average: 60)
Gender	6 male; 2 female
Number of Nights at Hotel	1–4 (average: 3)
Diabetes Mellitus	4
Immunocompromised	1
Smoker	5
Showered in Hotel	8
Used Hotel Whirlpool Spa	1
Used Hotel Swimming Pool	6



Gram stain showing bacteria within a tissue sample. LM 4 μm

Why is it important to identify the source?

6. Retrospective identification of cases allows control and remediation efforts. *L. pneumophila* of the same monoclonal antibody type was recovered from the hot water storage tanks, cooling tower, and showers and faucets in rooms occupied by patients and well guests.

   Why didn't other hotel guests get sick?

7. During outbreaks, attack rates tend to be highest in specific high-risk groups, including older adults, smokers, and immunocompromised persons.

   What are your recommendations for remediation?

Shower necks and faucets are disinfected with bleach. The spa filter was cleaned, and the potable water system is hyperchlorinated.

Hotels have been common locations for legionellosis outbreaks since the disease was first recognized among hotel guests in Philadelphia in 1976.

Source: Adapted from CDC data, 2010.

Diagnosis is usually made by isolating the pathogen from body fluids. Serological tests in endemic areas are problematic because of widespread exposure to a similar, nonpathogenic bacterium. A rapid PCR test is undergoing clinical testing. Treatment by antibiotic is uncertain in effectiveness; the most commonly used is ceftazidime, a β-lactam antibiotic, but months of treatment may be required.

CHECK YOUR UNDERSTANDING

- What group of bacterial pathogens causes what is informally called "walking pneumonia"? **24-7**
- The bacterium causing melioidosis in humans also causes a disease of horses known as what? **24-8**

Viral Diseases of the Lower Respiratory System

LEARNING OBJECTIVE

24-9 List the causative agent, symptoms, prevention, and preferred treatment for viral pneumonia, RSV, and influenza.

For a virus to reach the lower respiratory system and initiate disease, it must pass numerous host defenses designed to trap and destroy it. Nonetheless, numerous respiratory ailments are caused by viruses. A newly introduced test, the *xTAG respiratory panel,* can diagnose a dozen such ailments at a time.

Viral Pneumonia

Viral pneumonia can occur as a complication of influenza, measles, or even chickenpox. A number of enteric and other viruses have been shown to cause viral pneumonia, but viruses are isolated and identified in fewer than 1% of pneumonia-type infections because few laboratories are equipped to test clinical samples properly for viruses. In those cases of pneumonia for which no cause is determined, viral etiology is often assumed if mycoplasmal pneumonia has been ruled out.

In recent years, coronaviruses have emerged as causative agents of pneumonia. In 2003, **SARS-associated coronavirus (SARS)** emerged in Asia and spread to several countries. Since 2004, no known cases of SARS have been reported anywhere in the world. In 2012, **Middle East respiratory syndrome** coronavirus **(MERS-CoV)** was first reported in Saudi Arabia and then spread to several other countries. PCR is used to confirm SARS and MERS-CoV.

Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) is probably the most common cause of viral respiratory disease in infants. There are about 4500 deaths from RSV each year in the United States, mostly in infants 2 to 6 months old. It can also cause a life-threatening pneumonia in older adults, where it is easily misdiagnosed as influenza. Epidemics occur during the winter and early spring. Virtually all children become infected by age 2—of whom about 1% require hospitalization. We have previously mentioned that RSV is sometimes implicated in cases of otitis media. The name of the virus is derived from its characteristic of causing cell fusion (*syncytium* formation, Figure 15.7b, page 431) when grown in cell culture. The symptoms are coughing and wheezing that last for more than a week. Fever occurs only when there are bacterial complications. Several rapid serological tests are now available that use samples of respiratory secretions to detect both the virus and its antibodies.

Naturally acquired immunity is very poor. An immune globulin product has been approved to protect infants with lung problems that put them at high risk. Protective vaccines are being clinically tested. For chemotherapy in life-threatening situations, where its cost can be justified, the severity of symptoms can sometimes be reduced by aerosol administration of the antiviral drug ribavirin. The most recent approved treatment, usually reserved for high-risk patients, is the humanized monoclonal antibody, palivizumab (Synagis).

Influenza (Flu)

The developed countries of the world are probably more aware of **influenza (flu)** than any other disease, except the common cold. The flu is characterized by chills, fever, headache, and muscular aches. Recovery normally occurs in a few days, and coldlike symptoms appear as the fever subsides. Still, an estimated 30,000 to 50,000 Americans die annually of flu, even in nonepidemic years. Diarrhea is not a normal symptom of the disease, and the intestinal discomfort attributed to "stomach flu" is probably from some other cause.

The Influenza Virus

Viruses in the genus *Influenzavirus* consist of eight separate RNA segments of differing lengths enclosed by an inner layer of protein and an outer lipid bilayer (Figure 13.3b, page 361, and **Figure 24.14**). Embedded in the lipid bilayer are numerous projections that characterize the virus. There are two types of projections: *hemagglutinin (HA) spikes* and *neuraminidase (NA) spikes.*

The HA spikes, of which there are about 500 on each virus, allow the virus to recognize and attach to body cells before infecting them. Antibodies against the influenza virus are directed mainly at these spikes. The term *hemagglutinin* refers to the agglutination of red blood cells (hemagglutination) that occurs when the viruses are mixed with them. This reaction is important in serological tests, such as the hemagglutination inhibition test often used to identify the influenza virus and some other viruses.

The NA spikes, of which there are about 100 per virus, differ from the HA spikes in appearance and function. Apparently they enzymatically help the virus separate from the infected cell as the virus exits after intracellular reproduction. NA spikes also stimulate the formation of antibodies, but these are less important in the body's resistance to the disease than those produced in response to the HA spikes.

Clinical Case

The titers confirm Dr. Cantwell's suspicions that the Nguyen family has had psittacosis. The decreasing titers show they are recovering. Fewer than 50 cases of human psittacosis are reported each year. Infections may occur more often than reflected by reported cases for several reasons: (1) *C. psittaci* infections may be only mildly symptomatic; (2) physicians may not elicit a history of bird exposure when evaluating patients because they may not suspect the diagnosis or because patients may not recall transient bird exposure; (3) convalescent-phase serum samples may not be obtained on patients who show clinical improvement on therapy; and (4) prompt initiation of appropriate antibiotic therapy may blunt the antibody response to *C. psittaci,* making convalescent serologies unreliable.

Dr. Cantwell calls the Nguyen's veterinarian to obtain more information about Bitsy's death.

What does Dr. Cantwell need to know about Bitsy?

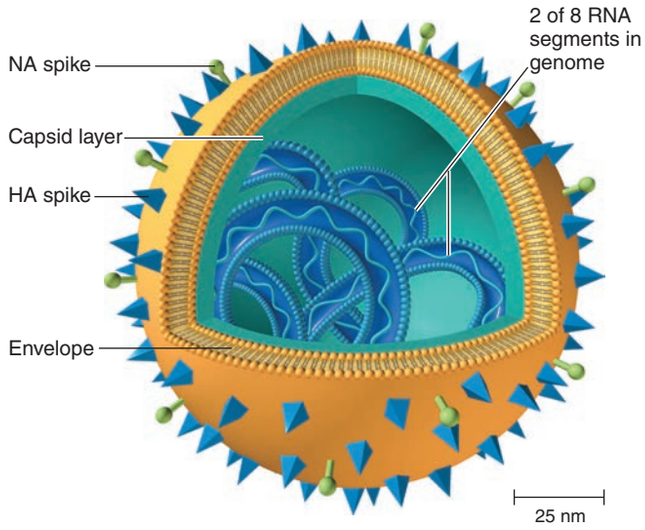


Figure 24.14 Detailed structure of the influenza virus. The virus is composed of a protein coat (capsid) that is covered by a lipid bilayer (envelope) and two types of spikes. The genome is composed of eight segments of RNA: six are devoted to internal proteins, and two are devoted to HA and NA spike proteins. Morphologically, under certain environmental conditions, the influenza virus assumes a filamentous form.

Q What is the primary antigenic structure on the influenza virus?

Viral strains are identified by variation in the HA and NA antigens. The different forms of the antigens are assigned numbers—for example HI, H2, H3, Nl, and N2. There are 16 subtypes of HA and 9 of NA. Each number change represents a substantial alteration in the protein makeup of the spike. These variations are determined by two processes, antigenic drift and antigenic shift. High mutation rates are a characteristic of RNA viruses, which lack the "proofreading" ability of DNA viruses. Accumulations of these mutations, **antigenic drift,** eventually allow the virus to elude much host immunity. The virus might still be designated as H2N2, for example, but viral strains arise that reflect minor antigenic changes. So far, the only truly human-adapted viruses are H1N1, H2N2, and H3N2. In an evolutionary sense, from the point of view of the virus it is desirable to accumulate mutations that favor transmission with minimal pathogenicity. (lf the virus quickly kills or makes the host bedridden, it is less likely to be transmitted.)

Antigenic shifts mark changes great enough to evade most of the immunity developed in the human population (see the Clinical Focus box in Chapter 13, page 364). This is responsible for the outbreaks, including the pandemics of 1918, 1957, and 1968, that are summarized in Table 24.1. Antigenic shifts involve a major genetic recombination, called *reassortment,* involving the eight segments of viral RNA (see Figure 24.14). To visualize reassortment, think of the symbols on the wheels of a slot machine.

The virus occurs in avian and mammalian strains; humans generally are not infected by avian strains. However, swine and many wild birds can be infected with both avian and mammalian strains of the influenza virus. Swine are, therefore, good "mixing vessels" in which reassortment occurs. Wild birds such as ducks and other migratory birds, infected with the virus, become symptomless carriers that spread the virus over large geographic areas. Communities in which humans, domestic chickens, and swine live in close proximity—primarily in east and southeast Asia—are where reassortment is most likely to occur. In these areas, poultry is now being produced in huge-scale farms that have become a breeding ground for outbreaks of avian influenza such as H5Nl, which appeared in China in the 1990s. Fortunately there has been only a very limited transmission of the virus from infected birds in these farms to humans. But there has been concern that reassortment might produce an avian H5 strain capable of rapid spread among the human population.

Epidemiology of Influenza

Almost every year, epidemics of the flu spread rapidly through large populations, although not always as a worldwide pandemic. The mortality rate from the disease is usually not high, less than 1%, and these deaths are mainly among the very young and the very old. However, so many people are infected in a major epidemic that the total number of deaths is often large.

TABLE 24.1 Human Influenza Viruses*

Type	Antigenic Subtype	Year	Disease Severity
A	H3N2 (the first "modern" pandemic; originated in southern China)	1889	Moderate
	H1N1 (Spanish)	1918	Severe
	H2N2 (Asian)	1957	Severe
	H3N2 (Hong Kong)	1968	Moderate
	H1N1 (Russian)†	1977	Low
	H1N1 (Mexico)‡	2009	Low
B	None	1940	Moderate
C	None	1947	Very mild

*The conventional wisdom is that H1, H2, and H3 are human-infecting strains; H4, H5, H6, and H7 primarily infect animals, especially swine and poultry. (Avian influenza strains H5N1 and H7N7 have caused human fatalities.)
†Probably escaped from a laboratory. At this time persons over age 20 were mostly immune from similar viruses circulating in the 1950s and earlier in the century.
‡The H1N1 virus causing this recent pandemic, the first in more than 40 years, differs significantly from the regular H1N1 virus that had been circulating. There has been confusion concerning a differentiating name for this virus. It has popularly been called the swine flu, and the CDC has referred to it as 2009H1N1, but in 2014 the WHO designed it as A(H1N1) pdm09.

Source: Adapted from C. Mims, J. Playfair, I. Roitt, D. Wakelin, and R. Williams, *Medical Microbiology,* 2nd ed. London: Mosby International, 1998.

The most recent pandemic, in 2009, involved an H1N1 virus. This strain is always of special interest because the lethal 1918 pandemic (see the following discussion) was caused by an H1N1 virus. Fortunately, the 2009 virus was not especially virulent. This strain had apparently been circulating indefinitely in pigs in Mexico and Central America and had not been detected because there was little surveillance in that area. Swine can function as something of a "warm freezer" for such a viral strain. Mutations of the influenza virus are more likely to occur in humans, who have a long life span. The virus must continue to mutate in order to evade accumulating immunological resistance. Swine and poultry, in contrast, have short life spans, especially if farm-reared, and the viruses infecting them are less likely to accumulate mutations. An H1N1 influenza virus, which has little pressure to mutate in farm-reared swine, tends to remain little changed in successive generations of the animal.

Influenza Vaccines

Thus far, it has not been possible to make a vaccine for influenza that gives long-term immunity to the general population. Although it isn't difficult to make a vaccine for a particular antigenic strain of virus, each new strain of circulating virus must be identified in time, usually about February, for the useful development and distribution of a new vaccine later that year. Strains of the influenza virus are collected in about 100 centers worldwide, then analyzed in central laboratories. This information is then used to decide on the composition of the vaccines to be offered for the next flu season. The vaccines are usually *multivalent*—directed at the three most important strains in circulation at the time. There are two types of vaccine available, an injected, inactivated version and a nasal-spray vaccine made with a live, attenuated virus.

A major problem is that production methods for vaccines require growing the virus in egg embryos. This process is labor intensive and also requires lead times of 6 to 9 months. The CDC is accelerating development of methods to shorten production times by several weeks in current egg-dependent systems. One way to accelerate development is to optimize the virus by selecting faster-growing strains. Another is to shorten the time now required to determine the amount of antigen in a vial of vaccine.

The use of eggs to create vaccines can be avoided by *cell-culture techniques,* in which the virus is grown in vats of cells derived from animal kidneys. This system is under development in Europe and is expected to shorten the vaccine's production time. However, any method that requires growth of viruses in either eggs or cells may still encounter unacceptably slow reproduction times.

The ultimate goal is a flu vaccine that will protect against all flu strains. An example would be to use a *conserved protein* as a target antigen. Such proteins are identical, or nearly so, in all flu viruses and are essential to the virus. Such a target might even not be in the virus itself, but might appear, for example, in the membrane of the infected cells. Therefore, targeting a conserved protein would lead to the destruction of the infected cells as well as the virus itself. Another example is in the hemagluttinin stalk. The globular head consists of proteins that change rapidly, whereas the stalk proteins, which are also necessary for infection, are conserved. In this example, the conserved proteins are not strongly antigenic, but molecules could be attached to them to provoke a stronger response.

The 1918–1919 Pandemic

In any discussion of influenza, the great pandemic of 1918–1919 must be mentioned.* Worldwide, 20 to 50 million people died, including an estimated 675,000 in the United States. No one is sure why it was so unusually lethal. Today, the very young and very old are the principal victims, but in 1918–1919, young adults had the highest mortality rate, often dying within a few hours, probably from a "cytokine storm." The infection is usually restricted to the upper respiratory system, but some change in virulence allowed the virus to invade the lungs and cause lethal hemorrhaging.

Evidence also suggests that the virus was able to infect cells in many organs of the body. In 2005, analysis of material preserved from the lungs of U.S. soldiers killed by the flu and from the exhumed body of a victim buried in permanently frozen soil in Alaska led to the complete genetic sequencing of the 1918 virus. The process of reverse genetics was then used to recreate the virus and grow it in chicken embryos and mice.

Bacterial complications also frequently accompanied the infection and, in those preantibiotic days, were often fatal. The 1918 viral strain apparently became endemic in the U.S. swine population and may have originated there. (See the Clinical Focus box in Chapter 13 on page 364.) Occasionally, influenza is still spread to humans from this reservoir, but the disease has not propagated as the virulent disease of 1918 did.

Diagnosis of Influenza

Influenza is difficult to diagnose reliably from clinical symptoms, which numerous respiratory diseases share. However, there are now several commercially available techniques that can diagnose influenza A and B within 20 minutes from a

*There will always be uncertainty concerning the origin of this most famous pandemic. The best reliable reports place the first well-documented cases among U.S. Army recruits at Camp Funston, Kansas, in March of 1918. The initial wave of influenza was a relatively mild illness that spread rapidly among the crowded troops and reached France as they were dispatched overseas. There the virus underwent a lethal mutation, seriously incapacitating troops on both sides of the front. Military censorship concealed this, and the first newspaper descriptions were published when the outbreak reached the population of neutral Spain, hence the name assigned to the pandemic: the **Spanish flu.** This second wave of influenza, with its high mortality, soon spread throughout the world and reentered the United States in the autumn and winter of 1918.

Clinical Case

Dr. Cantwell asks the Nguyens' veterinarian what, if any, symptoms Bitsy had before the decision was made to euthanize her and whether any tests were run on the bird after she was euthanized. The veterinarian consults his notes and tells Dr. Cantwell that chlamydial antigen was detected by ELISA from both cloacal (intestinal) and throat swabs of the euthanized cockatiel, but cultures for *C. psittaci* were not obtained.

Based on these results, what is the most likely mode of transmission, and how can transmission be prevented?

676 692 693 695 698 701

sample taken in a physician's office (from nasal washes or nasal swabs). A central laboratory with sophisticated equipment is required to identify viral strains.

Treatment of Influenza

The antiviral drugs amantadine and rimantadine significantly reduce the symptoms of influenza A if administered promptly. Two drugs for treatment of influenza have been introduced. They are inhibitors of neuraminidase, which the virus uses to separate itself from the host cell after it replicates. These are zanamivir (Relenza), which is inhaled, and oseltamivir (Tamiflu), which is administered orally. If taken within 30 hours of onset of influenza, these drugs slow replication. This action allows the immune system to be more effective, which shortens durations of symptoms and lowers the mortality rate. The bacterial complications of influenza are amenable to treatment with antibiotics.

CHECK YOUR UNDERSTANDING

Is reassortment of the RNA segments of the influenza virus the cause of antigenic shift or antigenic drift? **24-9**

Fungal Diseases of the Lower Respiratory System

LEARNING OBJECTIVE

24-10 List the causative agent, mode of transmission, preferred treatment, and laboratory identification tests for four fungal diseases of the respiratory system.

Fungi often produce spores that are disseminated through the air. It is therefore not surprising that several serious fungal diseases affect the lower respiratory system. The rate of fungal infections has been increasing in recent years. Opportunistic fungi are able to grow in immunosuppressed patients, and AIDS, transplant drugs, and anticancer drugs have created more immunosuppressed people than ever before.

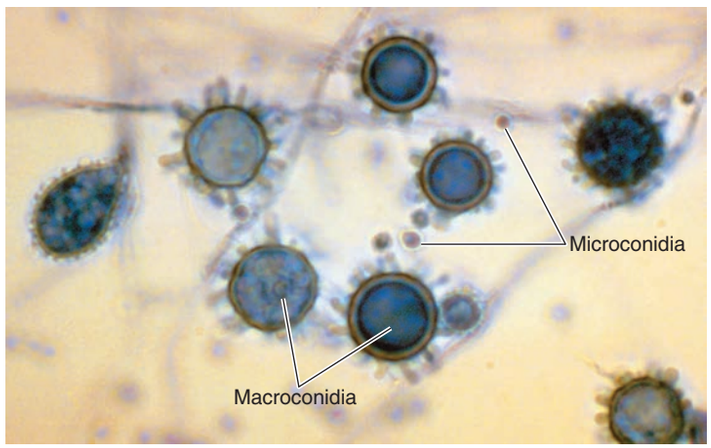
Histoplasmosis

Histoplasmosis superficially resembles tuberculosis. In fact, it was first recognized as a widespread disease in the United States when X-ray surveys showed lung lesions in many people who were tuberculin-test-negative. Although the lungs are most likely to be initially infected, the pathogens may spread in the blood and lymph, causing lesions in almost all organs of the body.

Symptoms are usually poorly defined and mostly subclinical, and the disease passes for a minor respiratory infection. In a few cases, perhaps fewer than 0.1%, histoplasmosis progresses, and it becomes a severe, generalized disease. This occurs with an unusually heavy inoculum or upon reactivation, when the infected person's immune system is compromised.

The causative organism, *Histoplasma capsulatum* (his-TŌ-plaz-mah kap-sū-LAH-tum), is a dimorphic fungus; that is, it has a yeastlike morphology in tissue growth, and, in soil or artificial media, it forms a filamentous mycelium carrying reproductive conidia (**Figure 24.15**). In the body, the yeastlike form is found intracellularly in macrophages, where it survives and multiplies.

Although histoplasmosis is rather widespread throughout the world, it has a limited geographic range in the United States (**Figure 24.16**). In general, the disease is found in the states adjoining the Mississippi and Ohio rivers. More than 75% of



The macroconidia of *Histoplasma capsulatum* are especially useful for diagnostic purposes. Microconidia bud off from hyphae and are the infectious form. At 37°C in tissues, the organism converts to a yeast phase composed of oval, budding yeasts.

Figure 24.15 ***Histoplasma capsulatum,*** **a dimorphic fungus that causes histoplasmosis.**

What does the term *dimorphic* mean?

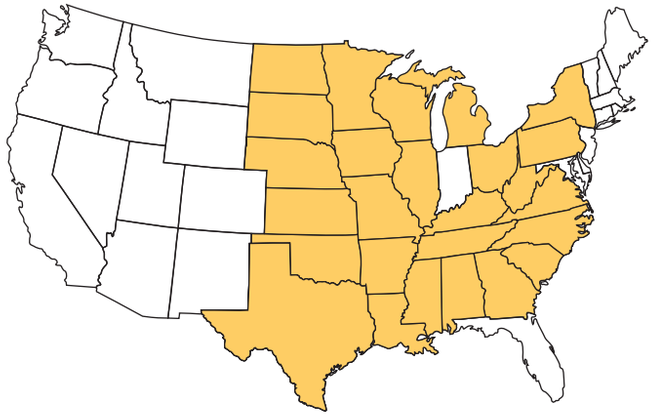


Figure 24.16 Histoplasmosis distribution. Gold indicates the U.S. geographic distribution.

Source: CDC.

Q Compared with the disease distribution shown in the map in Figure 24.18, what can you determine about the moisture requirements in the soil for the two fungi involved?

the population in some of these states have antibodies against the infection. In other states—Maine, for example—a positive test is a rare event. Approximately 50 deaths are reported in the United States each year from histoplasmosis.

Humans acquire the disease from airborne conidia produced under conditions of appropriate moisture and pH levels. These conditions occur especially where droppings from birds and bats have accumulated. Birds themselves, because of their high body temperature, do not carry the disease, but their droppings provide nutrients, particularly a source of nitrogen, for the fungus. Bats, which have a lower body temperature than birds, carry the fungus, shed it in their feces, and infect new soil sites.

Clinical signs and history, serological tests, DNA probes, and, most important, either isolating the pathogen or identifying it in tissue specimens are necessary for proper diagnosis. Currently, the most effective chemotherapy is amphotericin B or itraconazole.

Coccidioidomycosis

Another fungal pulmonary disease, also rather restricted geographically, is **coccidioidomycosis.** The causative agent is *Coccidioides immitis,* a dimorphic fungus. The arthroconidia are found in dry, alkaline soils of the American Southwest and in similar soils of South America and northern Mexico. Because of its frequent occurrence in the San Joaquin Valley of California, it is sometimes known as *Valley fever* or *San Joaquin fever.* In tissues, the organism forms a thick-walled body called a *spherule* filled with endospores (**Figure 24.17**). In soil, it forms filaments that reproduce by the formation of arthroconidia. The wind carries the arthroconidia to transmit the infection. Arthroconidia are often so abundant that simply driving through an endemic area can result in infection, especially during a dust storm. An estimated 100,000 infections occur each year.

Most infections are not apparent, and almost all patients recover in a few weeks, even without treatment. The symptoms of coccidioidomycosis include chest pain and perhaps fever, coughing, and weight loss. In less than 1% of cases,

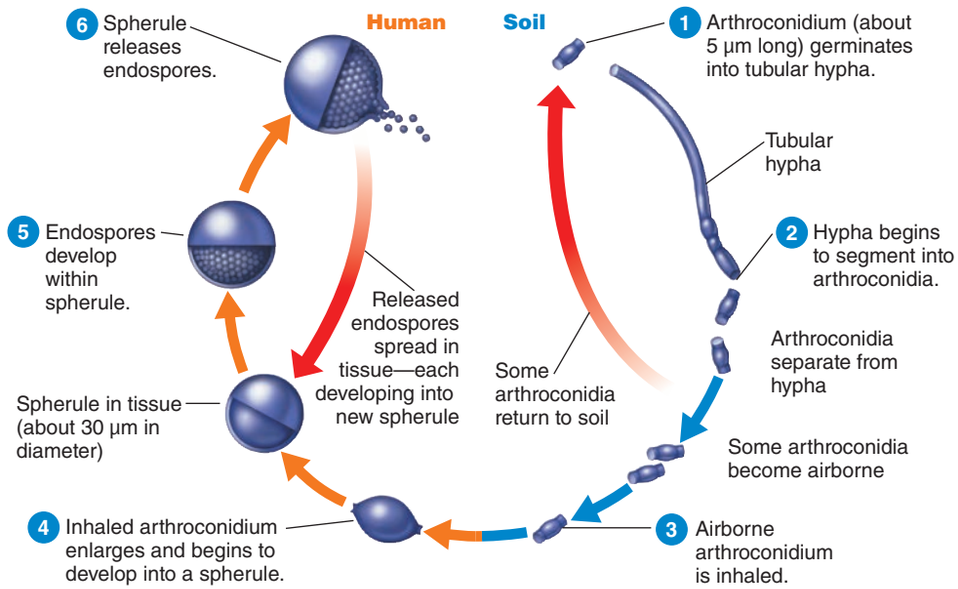


Figure 24.17 The life cycle of *Coccidioides immitis,* the cause of coccidioidomycosis.

Q What is the natural habitat of *Coccidioides*?

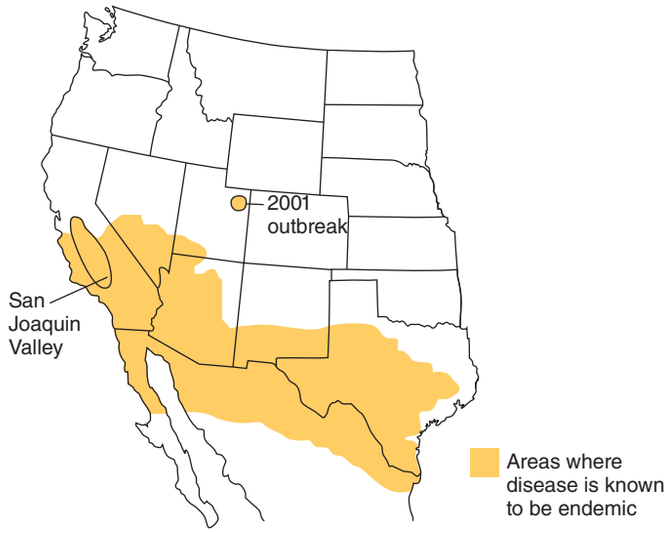


Figure 24.18 The U.S. endemic area for coccidioidomycosis. The outlined area in California is the San Joaquin Valley. Because of the very high incidence there, the disease is also sometimes called Valley fever. The small area on the map in northeastern Utah indicates an outbreak in 2001 in which ten archeologists working on excavations at the Dinosaur National Monument were infected.

Source: CDC.

Q Why does the incidence of coccidioidomycosis increase after ecological disturbances, such as earthquakes and construction?

a progressive disease resembling tuberculosis disseminates throughout the body. A substantial proportion of adults who are long-time residents of areas where the disease is endemic have evidence of prior infection with *C. immitis* by the skin test.

The incidence of coccidiodomycosis has been increasing recently in California and Arizona (**Figure 24.18**). Contributing factors include an increased number of older residents, and an increased prevalence of HIV/AIDS. Outbreaks may occur after an earthquake or other event that disturbs large amounts of soil. About 50 to 100 deaths occur annually from this disease in the United States.

Diagnosis is most reliably made by identifying the spherules in tissue or fluids. The organism can be cultured from fluids or lesions, but laboratory workers must use great care because of the possibility of infectious aerosols. Several serological tests and DNA probes are available for identifying isolates. A tuberculin-like skin test is used in screening.

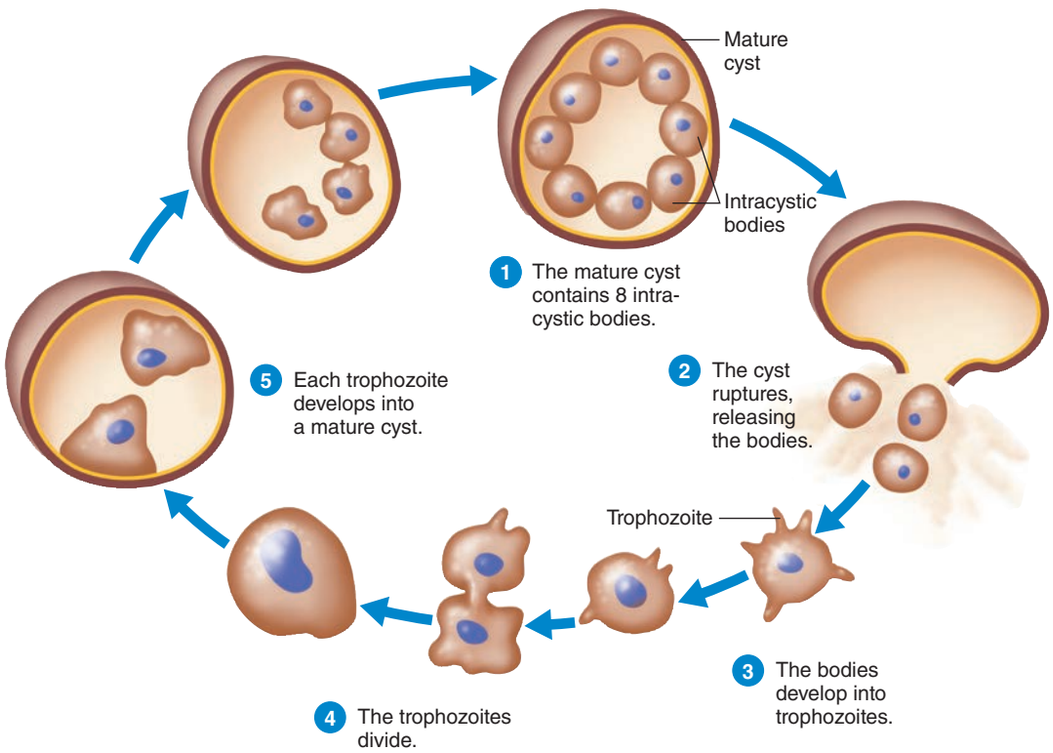
Amphotericin B has been used to treat serious cases. However, less toxic imidazole drugs, such as ketoconazole and itraconazole, are useful alternatives.

Pneumocystis Pneumonia

***Pneumocystis* pneumonia** is caused by *Pneumocystis jirovecii* (ye-rō-VET-zē-ē), formerly *P. carinii* (**Figure 24.19**). The taxonomic position of this microbe has been uncertain ever since its discovery in 1909, when it was thought to be a developmental

Figure 24.19 The life cycle of *Pneumocystis jirovecii*, the cause of *Pneumocystis* pneumonia. Long classified as a protozoan, this organism is now usually considered to be a fungus, but it has characteristics of both groups.

Q Of what value is proper classification of this organism?



stage of a trypanosome. Since that time, there has been no universal agreement about whether it is a protozoan or a fungus. It has some characteristics of both groups. Analysis of RNA and certain other structural characteristics indicate that it's closely related to certain yeasts, and it's usually reported as a fungus.

The pathogen is sometimes found in healthy human lungs. Immunocompetent adults have few or no symptoms, but newly infected infants occasionally show symptoms of a lung infection. Persons with compromised immunity are the most susceptible to symptomatic *Pneumocystis* pneumonia. This population may also be the reservoir of the organism, which is not found in the environment, animals, or very often in healthy humans. This portion of the population has also expanded greatly in recent decades. For example, before the AIDS epidemic, *Pneumocystis* pneumonia was an uncommon disease; perhaps 100 cases occurred each year. By 1993, it had become a primary indicator of AIDS, with more than 20,000 annual reported cases. Presumably, the loss of an effective immune defense allowed the activation of a latent infection. Other groups that are very susceptible to this disease are people whose immunity is depressed because of cancer or who are receiving immunosuppressive drugs to minimize rejection of transplanted tissue.

In the human lung, the microbes are found mostly in the lining of the alveoli. Diagnosis is usually made from sputum samples in which cysts are detected. There, they form a thick-walled cyst in which spherical intracystic bodies successively divide as part of a sexual cycle. The mature cyst contains eight such bodies (see Figure 24.19). Eventually the cyst ruptures and releases them, and each body develops into a trophozoite. The trophozoite cells can reproduce asexually by fission, but they may also enter the encysted sexual stage.

The drug of choice for treatment is currently trimethoprim-sulfamethoxazole, but there are several alternatives, such as clindamycin or intravenous pentamidine.

Blastomycosis (North American Blastomycosis)

Blastomycosis is usually called **North American blastomycosis** to differentiate it from a similar South American blastomycosis. It is caused by the fungus *Blastomyces dermatitidis* (blas′tō-MĪ-sēz der-mah-TI-ti-dis), a dimorphic fungus found most often in the Mississippi and Ohio river valleys, where it probably grows in soil. Approximately 30 to 60 deaths are reported each year, although most infections are asymptomatic.

The infection begins in the lungs. It resembles bacterial pneumonia and can spread rapidly. Cutaneous ulcers commonly appear, and there can be extensive abscess formation and tissue destruction. The pathogen can be isolated from pus and biopsy specimens. Amphotericin B or itraconazole is usually an effective treatment.

Other Fungi Involved in Respiratory Disease

Many other opportunistic fungi may cause respiratory disease, particularly in hosts who are immunosuppressed or have been exposed to massive numbers of spores. **Aspergillosis** is an important example; it is airborne by the conidia of *Aspergillus fumigatus* (FŪ-mi-gah-tus) and other species of *Aspergillus,* which are widespread in decaying vegetation. Compost piles are ideal sites for growth, and farmers and gardeners are most often exposed to infective amounts of these conidia.

Similar pulmonary infections sometimes result when individuals are exposed to spores of other mold genera, such as *Rhizopus* and *Mucor*. Such diseases can be very dangerous, particularly invasive infections of pulmonary aspergillosis. Predisposing factors include an impaired immune system, cancer, and diabetes. As with most systemic fungal infections, there is only a limited arsenal of antifungal agents available; amphotericin B has proved the most useful.

CHECK YOUR UNDERSTANDING

The droppings of both blackbirds and bats support the growth of *Histoplasma capsulatum;* which of these two animal reservoirs is normally actually infected by the fungus? **24-10**

* * *

Diseases in Focus 24.3 summarizes the microbial respiratory diseases affecting the lower respiratory system discussed in this chapter.

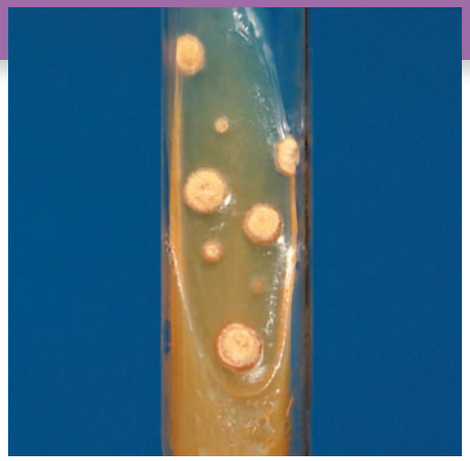
Clinical Case Resolved

Domestic and imported pet birds, as well as humans, are at risk for infection with and transmission of *C. psittaci* because shipping, crowding, and breeding promote shedding of the organism. Avian infection, which has a prevalence of less than 5%, may increase to 100% under such circumstances. The U.S. Department of Agriculture (USDA) requires a 30-day quarantine period for all imported birds to prevent the introduction of Newcastle disease (a viral disease that affects fowl); during this period, psittacine birds receive medicated chlortetracycline (CT) feed to prevent transmission of *C. psittaci* to USDA staff. Unless treatment is continued for 45 days, infected birds arriving to distributors from breeders and from quarantine may shed *C. psittaci* and continue to do so after purchase by consumers. Therefore, breeders and importers should ensure that all domestic nestlings and imported birds receive prophylactic CT for 45 continuous days to prevent future outbreaks of human psittacosis.

DISEASES IN FOCUS 24.3

Microbial Diseases of the Lower Respiratory System

Three weeks after working on the demolition of an abandoned building in Kentucky, a worker is hospitalized for acute respiratory illness. At the time of demolition, a colony of bats inhabited the building. An X-ray examination reveals a lung mass. A purified protein derivative test is negative; a cytological examination for cancer is also negative. The mass is surgically removed. Microscopic examination of the mass reveals ovoid yeast cells. Use the table below to make a differential diagnosis and identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Mycelial culture grown from the patient's lung mass.

Disease	Pathogen	Symptoms	Reservoir	Diagnosis	Treatment
BACTERIAL DISEASES					
Bacterial Pneumonia (see Diseases in Focus 24.2, page 691)					
Pertussis (whooping cough)	*Bordetella pertussis*	Spasms of intense coughing to clear mucus	Humans	Bacterial culture	Erythromycin Prevention: DTaP vaccine
Tuberculosis	*Mycobacterium tuberculosis* *M. bovis* *M. avium-intracellulare*	Cough, blood in mucus	Humans, cows: can be transmitted via unpasteurized milk	X-ray imaging; presence of acid-fast bacilli in sputum; tests for IFN-γ; PCR test for *M. tuberculosis*	Multiple-antimycobacterial drugs Prevention: pasteurizing milk; BCG vaccine
Melioidosis	*Burkholderia pseudomallei*	Pneumonia, or as tissue abscesses and severe sepsis	Moist soil	Bacterial culture	Ceftazidime
VIRAL DISEASES					
Respiratory Syncytial Virus (RSV) Disease	Respiratory syncytial virus	Pneumonia in infants	Humans	Serological tests	Palivizumab (if life-threatening)
Influenza	*Influenzavirus;* several serotypes	Chills, fever, headache, and muscular aches	Humans, pigs, birds	Serological EIA tests	Amantadine, oseltamivir phosphate (Tamiflu)
FUNGAL DISEASES					
Histoplasmosis	*Histoplasma capsulatum*	Resembles tuberculosis	Soil; widespread in Ohio and Mississippi river valleys	Serological tests	Amphotericin B
Coccidioidomycosis	*Coccidioides immitis*	Fever, coughing, weight loss	Desert soils of U.S. Southwest	Serological tests	Amphotericin B
***Pneumocystis* Pneumonia**	*Pneumocystis jirovecii*	Pneumonia	Unknown; possibly humans or soil	Microscopy	Trimethoprim-sulfamethoxazole, pentamidine
Blastomycosis	*Blastomyces dermatitidis*	Abscesses; extensive tissue damage	Soil in Mississippi Valley area	Isolation of pathogen	Amphotericin B

Study Outline

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Study microbiology where it matters: everywhere.
Check out the Study Area of MasteringMicrobiology to explore Interactive Microbiology. Study on-the-go with Dynamic Study Modules. Check your understanding with chapter quizzes and animations—and much more!

Introduction (p. 675)

1. Infections of the upper respiratory system are the most common type of infection.
2. Pathogens that enter the respiratory system can infect other parts of the body.

Structure and Function of the Respiratory System (pp. 676–677)

1. The upper respiratory system consists of the nose, pharynx, and associated structures, such as the middle ear and auditory tubes.
2. Coarse hairs in the nose filter large particles from air entering the respiratory tract.
3. The ciliated mucous membranes of the nose and throat trap airborne particles and remove them from the body.
4. Lymphoid tissue, tonsils, and adenoids provide immunity to certain infections.
5. The lower respiratory system consists of the larynx, trachea, bronchial tubes, and alveoli.
6. The ciliary escalator of the lower respiratory system helps prevent microorganisms from reaching the lungs.
7. Microbes in the lungs can be phagocytized by alveolar macrophages.
8. Respiratory mucus contains IgA antibodies.

Normal Microbiota of the Respiratory System (p. 677)

1. The normal microbiota of the nasal cavity and throat can include pathogenic microorganisms.
2. The lower respiratory system is usually sterile because of the action of the ciliary escalator.

Microbial Diseases of the Upper Respiratory System (pp. 677–681)

1. Specific areas of the upper respiratory system can become infected to produce pharyngitis, laryngitis, tonsillitis, sinusitis, and epiglottitis.
2. These infections may be caused by several bacteria and viruses, often in combination.
3. Most respiratory tract infections are self-limiting.
4. *H. influenzae* type b can cause epiglottitis.

Bacterial Diseases of the Upper Respiratory System (pp. 678–680)

Streptococcal Pharyngitis (Strep Throat) (p. 678)

1. This infection is caused by group A beta-hemolytic streptococci, the group that consists of *Streptococcus pyogenes.*
2. Symptoms of this infection are inflammation of the mucous membrane and fever; tonsillitis and otitis media may also occur.
3. Rapid diagnosis is made by enzyme immunoassays.
4. Immunity to streptococcal infections is type-specific.

Scarlet Fever (p. 678)

5. Strep throat, caused by an erythrogenic toxin-producing *S. pyogenes,* results in scarlet fever.
6. *S. pyogenes* produces erythrogenic toxin when lysogenized by a phage.
7. Symptoms include a red rash, high fever, and a red, enlarged tongue.

Diphtheria (pp. 678–679)

8. Diphtheria is caused by exotoxin-producing *Corynebacterium diphtheriae.*
9. Exotoxin is produced when the bacteria are lysogenized by a phage.
10. A membrane, containing fibrin and dead human and bacterial cells, forms in the throat and can block the passage of air.
11. The exotoxin inhibits protein synthesis, and heart, kidney, or nerve damage may result.
12. Laboratory diagnosis is based on isolation of the bacteria and the appearance of growth on differential media.
13. Routine immunization in the United States includes diphtheria toxoid in the DTaP vaccine.
14. Slow-healing skin ulcerations are characteristic of cutaneous diphtheria.
15. There is minimal dissemination of the exotoxin in the bloodstream.

Otitis Media (pp. 679–680)

16. Earache, or otitis media, can occur as a complication of nose and throat infections.
17. Pus accumulation causes pressure on the eardrum.
18. Bacterial causes include *Streptococcus pneumoniae,* non-encapsulated *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes,* and *Staphylococcus aureus.*

Viral Disease of the Upper Respiratory System (pp. 680–681)

The Common Cold (pp. 680–681)

1. Any one of approximately 200 different viruses can cause the common cold; rhinoviruses cause about 50% of all colds.
2. Rhinoviruses grow best slightly below body temperature.
3. The incidence of colds increases during cold weather, possibly because of increased interpersonal indoor contact or physiological changes.
4. Antibodies are produced against the specific viruses.

Microbial Diseases of the Lower Respiratory System (pp. 681–702)

1. Many of the same microorganisms that infect the upper respiratory system also infect the lower respiratory system.
2. Diseases of the lower respiratory system include bronchitis and pneumonia.

Bacterial Diseases of the Lower Respiratory System (pp. 681–694)

Pertussis (Whooping Cough) (pp. 681–684)

1. Pertussis is caused by *Bordetella pertussis.*
2. The initial stage of pertussis resembles a cold and is called the catarrhal stage.
3. The accumulation of mucus in the trachea and bronchi causes deep coughs characteristic of the paroxysmal (second) stage.
4. The convalescence (third) stage can last for months.
5. Regular immunization for children has decreased the incidence of pertussis.

Tuberculosis (pp. 684–689)

6. Tuberculosis is caused by *Mycobacterium tuberculosis.*
7. *Mycobacterium bovis* causes bovine tuberculosis and can be transmitted to humans by unpasteurized milk.
8. *M. avium-intracellulare* complex infects patients in the late stages of HIV infection.
9. *M. tuberculosis* may be ingested by alveolar macrophages; if not killed, the bacteria reproduce in the macrophages.
10. Lesions formed by *M. tuberculosis* are called tubercles; dead macrophages and bacteria form the caseous lesion that might calcify and appear in an X-ray image as a Ghon's complex.
11. Liquefaction of the caseous lesion results in a tuberculous cavity in which *M. tuberculosis* can grow.
12. New foci of infection can develop when a caseous lesion ruptures and releases bacteria into blood or lymph vessels; this is called miliary tuberculosis.
13. A positive tuberculin skin test can indicate either an active case of TB, prior infection, or vaccination and immunity to the disease.
14. Active infections can be diagnosed by detection of IFN-γ or rapid PCR test for *M. tuberculosis.*
15. Chemotherapy usually involves three or four drugs taken for at least 6 months; multidrug-resistant *M. tuberculosis* is becoming prevalent.
16. BCG vaccine for tuberculosis consists of a live, avirulent culture of *M. bovis.*

Bacterial Pneumonias (pp. 689–693)

17. Typical pneumonia is caused by *S. pneumoniae.*
18. Atypical pneumonias are caused by other microorganisms.
19. Pneumococcal pneumonia is caused by encapsulated *Streptococcus pneumoniae.*
20. Alcoholism, poor nutrition, cancer, and diabetes are predisposing factors for *H. influenzae* pneumonia.
21. *Mycoplasma pneumoniae* causes mycoplasmal pneumonia; it is an endemic disease.
22. Legionellosis is caused by the aerobic gram-negative rod *Legionella pneumophila.*
23. *Chlamydophila psittaci,* the bacterium that causes psittacosis (ornithosis), is transmitted by contact with contaminated droppings and exudates of fowl.
24. *Chlamydophila pneumoniae* causes pneumonia; it is transmitted from person to person.
25. Obligately parasitic, intracellular *Coxiella burnetii* causes Q fever.

Melioidosis (pp. 693–694)

26. Melioidosis, caused by *Burkholderia pseudomallei,* is transmitted by inhalation, ingestion, or through puncture wounds. Symptoms include pneumonia, sepsis, and encephalitis.

Viral Diseases of the Lower Respiratory System (pp. 694–698)

Viral Pneumonia (p. 695)

1. A number of viruses can cause pneumonia as a complication of infections such as influenza.
2. The etiologies are not usually identified in a clinical laboratory because of the difficulty in isolating and identifying viruses.

Respiratory Syncytial Virus (RSV) (p. 695)

3. RSV is the most common cause of pneumonia in infants.

Influenza (Flu) (pp. 695–698)

4. Influenza is caused by *Influenzavirus* and is characterized by chills, fever, headache, and general muscular aches.
5. Hemagglutinin (HA) and neuraminidase (NA) spikes project from the outer lipid bilayer of the virus.
6. Viral strains are identified by antigenic differences in the HA and NA spikes; they are also divided by antigenic differences in their protein coats (A, B, and C).
7. Viral isolates are identified by hemagglutination-inhibition tests and immunofluorescence testing with monoclonal antibodies.
8. Antigenic shifts that alter the antigenic nature of the HA and NA spikes make natural immunity of questionable value. Minor antigenic changes are caused by antigenic drift.
9. Deaths during an influenza epidemic are usually from secondary bacterial infections.
10. Multivalent vaccines are available for older adults and other high-risk groups.
11. Amantadine and rimantadine are effective prophylactic and curative drugs against influenza A virus.

Fungal Diseases of the Lower Respiratory System (pp. 698–702)

1. Fungal spores are easily inhaled; they may germinate in the lower respiratory tract.
2. The incidence of fungal diseases has been increasing in recent years.
3. The mycoses in the following sections can be treated with amphotericin B.

Histoplasmosis (pp. 698–699)

4. *Histoplasma capsulatum* causes a subclinical respiratory infection that only occasionally progresses to a severe, generalized disease.
5. The disease is acquired by inhaling airborne conidia.
6. Isolating or identifying the fungus in tissue samples is necessary for diagnosis.

Coccidioidomycosis (pp. 699–700)

7. Inhaling the airborne arthroconidia of *Coccidioides immitis* can result in coccidioidomycosis.

***Pneumocystis* Pneumonia** (pp. 700–701)

8. *Pneumocystis jirovecii* is found in healthy human lungs.

9. *P. jirovecii* causes disease in immunosuppressed patients.

Blastomycosis (North American Blastomycosis) (p. 701)

10. *Blastomyces dermatitidis* is the causative agent of blastomycosis.

11. The infection begins in the lungs and can spread to cause extensive abscesses.

Other Fungi Involved in Respiratory Disease (pp. 701–702)

12. Opportunistic fungi can cause respiratory disease in immunosuppressed hosts, especially when large numbers of spores are inhaled.

13. Among these fungi are *Aspergillus, Rhizopus,* and *Mucor.*

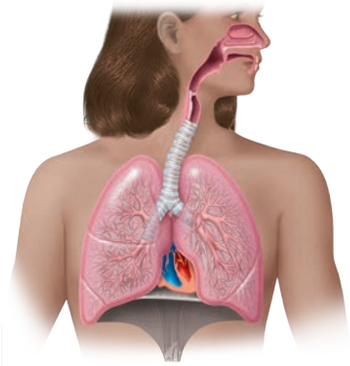
Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. DRAW IT Show the location of the following diseases: common cold, diphtheria, coccidioidomycosis, influenza, pneumonia, scarlet fever, tuberculosis, whooping cough



2. Compare and contrast mycoplasmal pneumonia and viral pneumonia.

3. List the causative agent, symptoms, and treatment for four viral diseases of the respiratory system. Separate the diseases according to whether they infect the upper or lower respiratory system.

4. Complete the following table.

Disease	Causative Agent	Symptoms	Treatment
Streptococcal pharyngitis			
Scarlet fever			
Diphtheria			
Whooping cough			
Tuberculosis			
Pneumococcal pneumonia			
H. influenzae pneumonia			
Chlamydial pneumonia			
Otitis media			
Legionellosis			
Psittacosis			
Q fever			
Epiglottitis			
Melioidosis			

5. Under what conditions can the saprophytes *Aspergillus* and *Rhizopus* cause infections?

6. A patient has been diagnosed as having pneumonia. Is this sufficient information to begin treatment with antimicrobial agents? Briefly discuss why or why not.

7. List the causative agent, mode of transmission, and endemic area for the diseases histoplasmosis, coccidioidomycosis, blastomycosis, and *Pneumocystis* pneumonia.

8. Briefly describe the procedures and positive results of the tuberculin test and what is indicated by a positive test.

9. Identify the bacteria involved in respiratory infections using the following laboratory test results:

Gram-positive cocci
- Catalase-positive: a. _____
- Catalase-negative
  - Beta-hemolytic, bacitracin inhibition: b. _____
  - Alpha-hemolytic, optochin inhibition: c. _____

Gram-positive rods
- Non–acid-fast: d. _____
- Acid-fast: e. _____

Gram-negative cocci: f. _____

Gram-negative rods
- Aerobes
  - Coccobacilli: g. _____
  - Rods
    - Grow on nutrient agar: h. _____
    - Require special media: i. _____
- Facultative anaerobes
  - Coccobacilli: j. _____
- Intracellular parasites
  - Form elementary bodies: k. _____
  - Do not form elementary bodies: l. _____
- Wall-less: m. _____

10. NAME IT These aerobic, gram-negative bacteria produce tracheal cytotoxin that kills ciliated cells of the trachea.

Multiple Choice

1. A patient has fever, difficulty breathing, chest pains, fluid in the alveoli, and a positive tuberculin skin test. Gram-positive cocci are isolated from the sputum. The recommended treatment is

a. fluoroquinolone.
b. antitoxin.
c. isoniazid.
d. tetracyclines.
e. none of the above.

2. No bacterial pathogen can be isolated from the sputum of a patient with pneumonia. Antibiotic therapy has not been successful. The next step should be
   a. culturing for *Mycobacterium tuberculosis.*
   b. culturing for *Mycoplasma pneumoniae.*
   c. culturing for fungi.
   d. a change in antibiotics.
   e. none; nothing more can be done.

Match the following choices to the culture descriptions in questions 3 through 6:

a. *Chlamydophila*
b. *Coccidioides*
c. *Histoplasma*
d. *Mycobacterium*
e. *Mycoplasma*

3. Your culture from a pneumonia patient appears not to have grown. You do see colonies, however, when the plate is viewed at 100×.
4. This pneumonia etiology requires cell culture.
5. Microscopic examination of a lung biopsy shows ovoid cells in macrophages. You suspect these are the cause of the patient's symptoms, but your culture grows a filamentous organism.
6. Microscopic examination of a lung biopsy shows spherules.
7. In San Francisco, ten animal health care technicians developed pneumonia 2 weeks after 130 goats were moved to the animal shelter where they worked. Which of the following is *false*?
   a. Diagnosis is made by a blood agar culture of sputum.
   b. The cause is *Coxiella burnetii.*
   c. The bacteria produce endospores.
   d. The disease was transmitted by aerosols.
   e. Diagnosis is made by complement-fixation tests for antibodies.
8. Which of the following leads to all the rest?
   a. catarrhal stage
   b. cough
   c. loss of cilia
   d. mucus accumulation
   e. tracheal cytotoxin

Match the following choices to the statements in questions 9 and 10:

a. *Bordetella pertussis*
b. *Corynebacterium diphtheriae*
c. *Legionella pneumophila*
d. *Mycobacterium tuberculosis*
e. none of the above

9. Causes the formation of a membrane across the throat.
10. Resistant to destruction by phagocytes.

Analysis

1. Differentiate *S. pyogenes* causing strep throat from *S. pyogenes* causing scarlet fever.
2. Why might the influenza vaccine be less effective than other vaccines?
3. Explain why it would be impractical to include cold and influenza vaccinations in the required childhood vaccinations.

Clinical Applications and Evaluation

1. In August, a 24-year-old man from Virginia developed difficulty breathing and bilateral lobe infiltrates 2 months after driving through California. During initial evaluation, typical pneumonia was suspected, and he was treated with antibiotics. Efforts to diagnose the pneumonia were unsuccessful. In October, a laryngeal mass was detected, and laryngeal cancer was suspected; treatment with steroids and bronchodilators did not result in improvement. Lung biopsy and laryngoscopy detected diffuse granular tissue. He was treated with amphotericin B and discharged after 5 days. What was the disease? What might have been done differently to decrease the patient's recovery time from 3 months to 1 week?
2. During a 6-month period, 72 clinic staff members became tuberculin-positive. A case-control study was undertaken to determine the most likely source of *M. tuberculosis* infection among the staff. A total of 16 cases and 34 tuberculin-negative controls were compared. Pentamidine isethionate is not used for TB treatment. What disease was probably being treated with this drug? What is the most likely source of infection?

	Cases	Control
Works ≥40 hr/week	100%	62%
In room during aerosolized pentamidine isethionate therapy in TB patients	31	3
Patient contact	94	94
Lunch eaten in staff lounge	38	35
Resident of western Palm Beach	75	65
Female	81	77
Cigarette smoker	6	15
Contact with nurse diagnosed with TB	15	12
In unventilated room during collection of TB-positive sputum samples	13	8

3. In a 2-week period, eight infants in an intensive care nursery (ICN) developed pneumonia caused by RSV. Complement-fixation (CF) screening and ELISA for viral antigens were performed to diagnose infections. RSV-positive patients were placed in a separate room. A 2-week-old girl from the newborn nursery, adjacent to the ICN, also developed an RSV infection. Toward the end of this outbreak, CF tests and direct ELISA tests were made of ten ICN staff members. ELISA–viral antigen tests were negative; RSV titers as determined by CF are shown below.

Staff	RSV Titer
A	0
B	64
C	32
D	128
E	256
F	0
G	0
H	32
I	32
J	16

Comment on the probable source of this outbreak. Explain the apparent discrepancy between the CF test and ELISA results. How can RSV infections in nurseries be prevented?



In the Clinic

As the county public health nurse, you were contacted regarding a woman who had acute gastroenteritis after dining at a local restaurant with friends. You interviewed the diners and confirmed that three of the seven in the party had consumed New England clam chowder. Within 1 to 4 hours after consumption, the three had onset of nausea and vomiting lasting 24 to 48 hours. The four diners who had not eaten the clam chowder did not become ill. The restaurant had kept the clam chowder at 39°C for the lunch and dinner service. **What microbial etiology is most likely?**

Hint: Make a list of the foodborne diseases covered in this chapter to match to this case.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

25

Microbial Diseases of the Digestive System

Microbial diseases of the digestive system are second only to respiratory diseases as causes of illness in the United States. Most such diseases result from ingesting food or water contaminated with pathogenic microorganisms or their toxins. These pathogens usually enter the food or water supply after being shed in the feces of people or animals infected with them. Therefore, microbial diseases of the digestive system are typically transmitted by a **fecal–oral cycle.** This cycle is interrupted by effective sanitation practices in food production and handling. Modern methods of sewage treatment and disinfection of water are essential. There is also an increasing awareness of the need for new tests that will rapidly and reliably detect pathogens in foods (a perishable commodity).

The Centers for Disease Control and Prevention (CDC) estimates that about 76 million cases of foodborne disease resulting in about 5000 deaths occur annually in the United States. As more of our food products—especially fruits and vegetables—are grown in countries with poor sanitation standards, outbreaks of foodborne disease from imported pathogens are expected to increase. Some *Escherichia coli* cause disease by making a toxin called Shiga toxin. The bacteria (shown in the photo) that make these toxins are called Shiga toxin-producing *E. coli* (STEC). An STEC infection is described in the Clinical Case in this chapter.

***Escherichia coli* bacteria are essential members of the microbiota unless they produce a toxin, such as the Shiga toxin produced by *E. coli* O157:H7.**

Structure and Function of the Digestive System

LEARNING OBJECTIVE

25-1 Name the structures of the digestive system that contact food.

The **digestive system** is essentially a tubelike structure, the *gastrointestinal (GI) tract* or *alimentary canal*—mainly the mouth, pharynx (throat), esophagus (food tube leading to the stomach), stomach, and the small and large intestines. It also includes *accessory structures* such as the teeth and tongue. Certain other accessory structures such as the salivary glands, liver, gallbladder, and pancreas lie outside the GI tract and produce secretions that are conveyed by ducts into it (**Figure 25.1**).

The purpose of the digestive system is to digest foods—that is, to break them down into small molecules that can be taken up and used by body cells. In a process called *absorption,* these end-products of digestion pass from the small intestine into the blood or lymph for distribution to body cells. Then the food moves through the large intestine, where water, vitamins, and nutrients are absorbed from it. Over the course of an average life span, about 25 tons of food pass through the GI tract. The resulting undigested solids, called *feces,* are eliminated from the body through the anus. Intestinal gas, or *flatus,* is a mixture of nitrogen from swallowed air and microbially produced carbon dioxide, hydrogen, and methane. On average, we produce 0.5 to 2.0 liters of flatus every day.

There is also a relationship between the body's digestive system and immune system. The first bacteria that colonize an infant's gastrointestinal tract make the immune response more favorable for their own survival, because the immune system then reacts against harmful antigens and ignores those that are not. Throughout life, the intestinal mucosa continues to be challenged by the antigens of the intestinal microbiota and ingested food. As a consequence, an estimated 80% of the immune system is located in the intestinal tract, especially the small intestine. This loosely organized lymphoid tissue and structures such as lymph nodes and Peyer's patches are collectively called *gut-associated lymphoid tissue (GALT).*

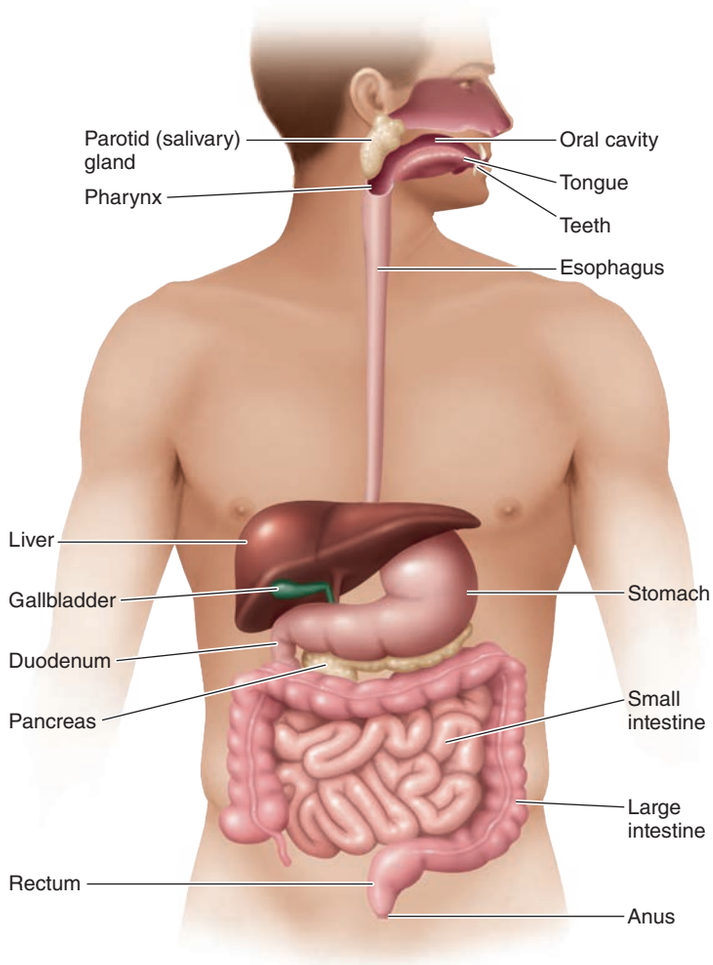


Figure 25.1 The human digestive system.

Q Where are microorganisms normally found in the digestive system?

Clinical Case: A Birthday Surprise

Nadia Abramovic is worried about her 5-year-old daughter, Anna. The week started out like any other; as a matter of fact, Anna was still talking about her birthday party the weekend before. But for the past two days, Anna has been pale and listless and complaining that her stomach hurts. When she sees that Anna has slimy, bloody diarrhea, Mrs. Abramovic immediately calls the pediatrician's office to make an appointment. Anna's pediatrician sends a stool sample to the local laboratory for a bacterial culture.

How will the laboratory test for the etiology of Anna's illness? Read on to find out.

708 718 724 731 739

CHECK YOUR UNDERSTANDING

✓ Small explosions have occurred when a surgeon used spark-producing instruments to remove intestinal polyps. What ignited? **25-1**

Normal Microbiota of the Digestive System

LEARNING OBJECTIVE

25-2 Identify parts of the gastrointestinal tract that normally have microbiota.

Bacteria heavily populate most of the digestive system. In the mouth, each milliliter of saliva can contain millions of bacteria.

The stomach and small intestine have relatively few microorganisms because of the hydrochloric acid produced by the stomach and the rapid movement of food through the small intestine. By contrast, the large intestine has enormous microbial populations, exceeding 100 billion bacteria per gram of feces. (Up to 40% of fecal mass is microbial cell material.) The population of the large intestine is composed mostly of anaerobes and facultative anaerobes. Most of these bacteria assist in the enzymatic breakdown of foods, especially many polysaccharides that would otherwise be indigestible. Some of them synthesize useful vitamins.

It's important to understand that food passing through the tubelike GI tract, although it's in contact with the body, remains outside the body. Unlike the body's exterior, such as the skin, the GI tract is adapted to absorbing nutrients passing through it. However, at the same time that nutrients are absorbed from the GI tract, harmful microbes ingested in food and water must be kept from invading the body. An important factor in this defense is the high acid content of the stomach, which eliminates many potentially harmful ingested microbes.

The small intestine also contains important antimicrobial defenses, most significantly, millions of specialized, granule-filled cells called *Paneth cells.* These are capable of phagocytizing bacteria, and they also produce antibacterial proteins called *defensins* (see antimicrobial peptides, page 462) and the antibacterial enzyme *lysozyme.*

CHECK YOUR UNDERSTANDING

How are normal microbiota confined to the mouth and large intestine? **25-2**

Bacterial Diseases of the Mouth

LEARNING OBJECTIVE

25-3 Describe the events that lead to dental caries and periodontal disease.

The mouth, which is the entrance to the digestive system, provides an environment that supports a large and varied microbial population.

Dental Caries (Tooth Decay)

The teeth, unlike any other exterior surface of the body, are hard and do not shed surface cells (**Figure 25.2**). This allows masses of microorganisms and their products to accumulate. These accumulations, called **dental plaque,** are a type of biofilm (see page 156 in Chapter 6) and are intimately involved in the formation of **dental caries,** or tooth decay.

Oral bacteria convert sucrose and other carbohydrates into lactic acid, which in turn attacks the tooth enamel. The microbial population on and around the teeth is very complex. Based on ribosomal identification methods (see the discussion of FISH on page 283 in Chapter 10), over 700 species of bacteria have been identified in the oral cavity. Probably the most important *cariogenic* (caries-causing) bacterium is *Streptococcus mutans,* a gram-positive coccus that has important virulence characteristics (**Figure 25.3a**). *S. mutans* is capable of metabolizing a wide range of carbohydrates, tolerates a high level of acidity, and synthesizes *dextran,* a gummy polysaccharide of glucose molecules which is an important factor in the formation of dental plaque (Figure 25.3b). Some other species of streptococci are also cariogenic but play a lesser role in initiating caries.

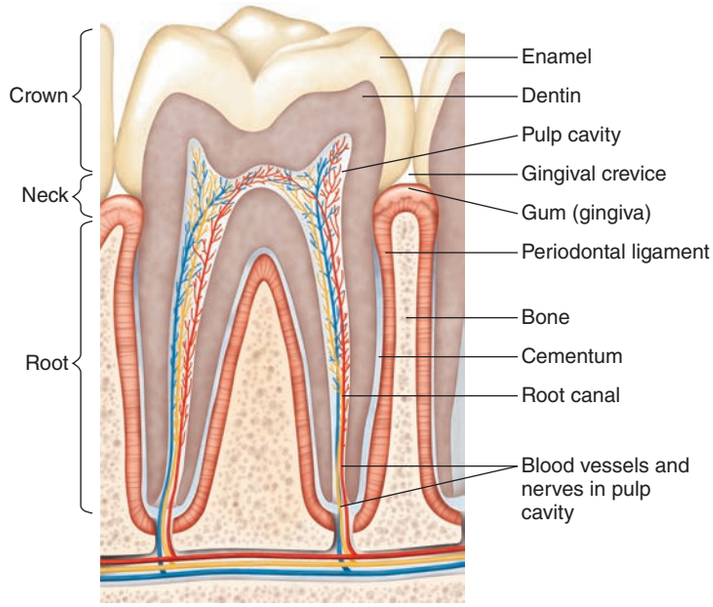
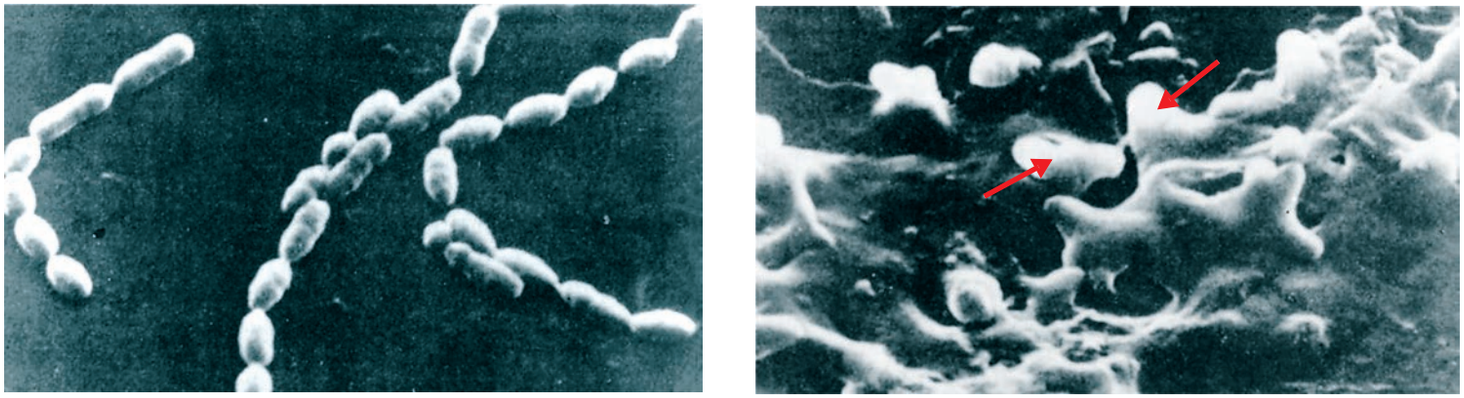


Figure 25.2 A healthy human tooth.

Why can a biofilm accumulate on teeth?

The initiation of caries depends on the attachment of *S. mutans* or other streptococci to the tooth. These bacteria don't adhere to a clean tooth, but a freshly brushed tooth will become coated with a pellicle (thin film) of proteins from saliva within minutes. Within a couple of hours, cariogenic bacteria become established on this pellicle and begin to produce dextran (see Figure 25.3b). In the production of dextran, the bacteria first hydrolyze sucrose into its component monosaccharides, fructose and glucose. The enzyme glucosyltransferase then assembles the glucose molecules into dextran. The residual fructose is the primary sugar fermented into lactic acid. Accumulations of bacteria and dextran adhering to the teeth make up dental plaque.

The bacterial population of plaque may harbor over 400 bacterial species but is predominantly streptococci and filamentous members of the genus *Actinomyces.* (Older, calcified deposits of plaque are called *dental calculus,* or *tartar.*) *S. mutans* especially favors crevices or other sites on the teeth protected from the shearing action of chewing or the flushing action of the liter or so of saliva produced in the mouth each day. On protected areas of the teeth, plaque accumulations



(a) *S. mutans* growing in glucose broth

(b) *S. mutans* growing in sucrose broth; note the accumulations of dextran. Arrows point to *S. mutans* cells.

Figure 25.3 ***Streptococcus mutans.*** The dextran allows *S. mutans* to adhere to teeth.

Q What makes dental plaque a type of biofilm?

can be several hundred cells thick. Because plaque is not very permeable to saliva, the lactic acid produced by bacteria isn't diluted or neutralized, and it breaks down the enamel of the teeth to which the plaque adheres.

Although saliva contains nutrients that encourage the growth of bacteria, it also contains antimicrobial substances, such as *lysozyme,* that help protect exposed tooth surfaces. Some protection is also provided by *crevicular fluid,* a tissue exudate that flows into the gingival crevice (see Figure 25.2) and is closer in composition to serum than saliva. It protects teeth by virtue of its flushing action, its phagocytic cells, and immunoglobulin content.

Localized acid production within deposits of dental plaque results in a gradual softening of the external *enamel.* Enamel low in fluoride is more susceptible to the effects of the acid. This is the reason for fluoridation of water and toothpastes, a significant factor in the decline in tooth decay in the United States.

The stages of tooth decay are shown in **Figure 25.4**. If the initial penetration of the enamel by caries remains untreated, bacteria can penetrate into the interior of the tooth. The composition of the bacterial population involved in spreading the decayed area from the enamel into the *dentin* is entirely different from that of the population initiating the decay. The dominant microorganisms are gram-positive rods and filamentous bacteria; *S. mutans* is present in small numbers. Although once considered the cause of dental caries, *Lactobacillus* spp. actually play no role in initiating the process. However, these very prolific lactic acid producers are important in advancing the front of the decay once it has become established.

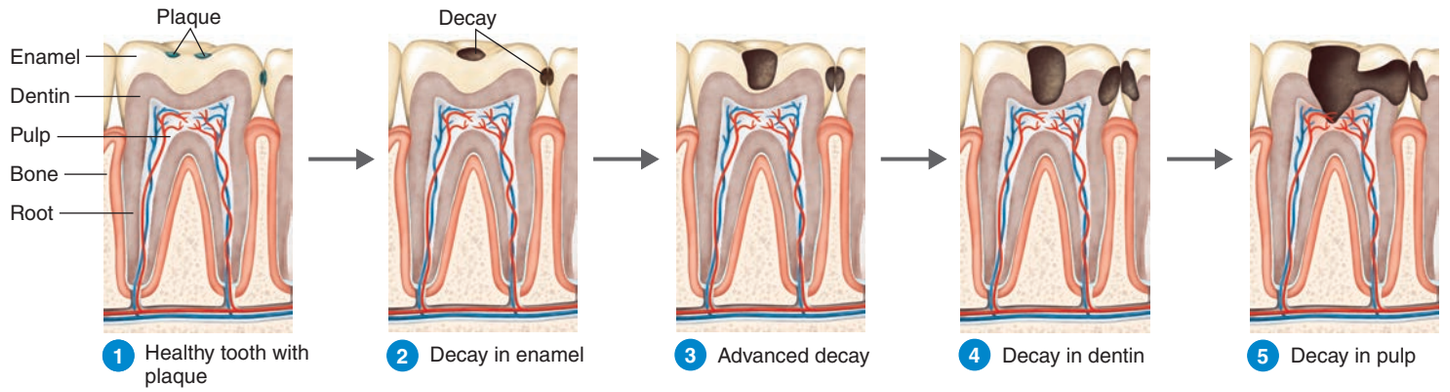


Figure 25.4 **The stages of tooth decay.** 1 A tooth with plaque accumulation in difficult-to-clean areas. 2 Decay begins as enamel is attacked by acids formed by bacteria. 3 Decay advances through the enamel. 4 Decay advances into the dentin. 5 Decay enters the pulp and may form abscesses in the tissues surrounding the root.

Q How does the formation of plaque contribute to tooth decay?

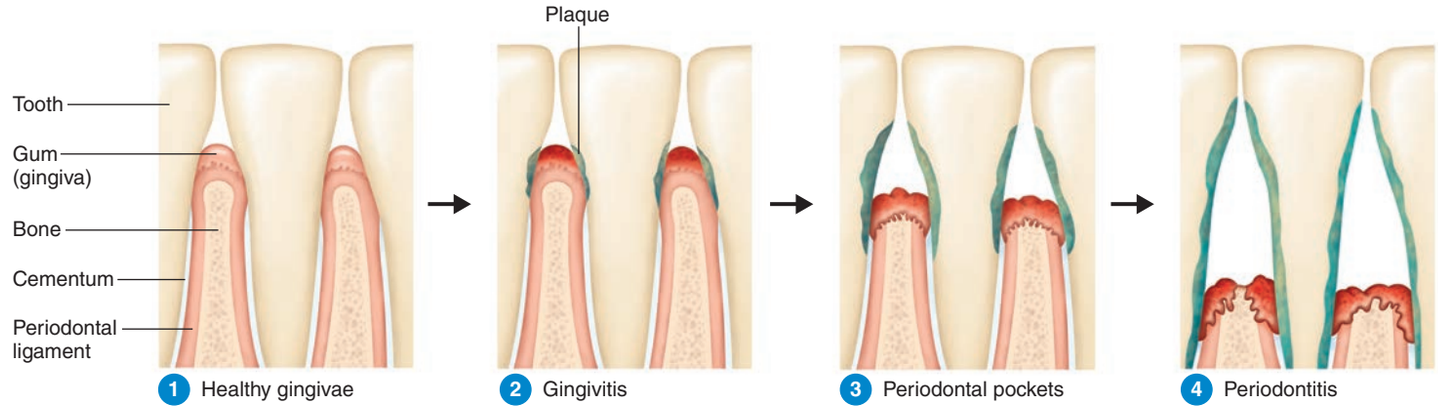


Figure 25.5 The stages of periodontal disease. 1 Teeth firmly anchored by healthy bone and gum tissue (gingiva). 2 Toxins in plaque irritate gums, causing gingivitis. 3 Periodontal pockets form as the tooth separates from the gingiva. 4 Gingivitis progresses to periodontitis. Toxins destroy the gingiva and bone that support the tooth and the cementum that protects the root.

Q What is the cause of "pink tooth brush"?

The decayed area eventually advances to the *pulp* (see Figure 25.4), which connects with the tissues of the jaw and contains the blood supply and the nerve cells. Almost any member of the normal microbiota of the mouth can be isolated from the infected pulp and roots. Once this stage is reached, root canal therapy is required to remove the infected and dead tissue and to provide access for antimicrobial drugs that suppress renewed infection. If untreated, the infection may advance from the tooth to the soft tissues, producing dental abscesses caused by mixed bacterial populations that contain many anaerobes.

Although dental caries is probably one of the more common infectious diseases in humans today, it was scarce in the Western world until about the seventeenth century. In human remains from older times, only about 10% of the teeth contain caries. The introduction of table sugar, or sucrose, into the diet is highly correlated with our present level of caries in the Western world. Studies have shown that sucrose, a disaccharide composed of glucose and fructose, is much more cariogenic than either glucose or fructose individually (see Figure 25.3). People living on high-starch diets (starch is a polysaccharide of glucose) have a low incidence of tooth decay unless sucrose is also a significant part of their diet. The contribution of bacteria to tooth decay has been shown by experiments with germ-free animals. Such animals don't develop caries even when fed a sucrose-rich diet designed to encourage their formation.

Sucrose is pervasive in the modern Western diet. However, if sucrose is ingested only at regular mealtimes, the protective and repair mechanisms of the body are usually not overwhelmed. It is the sucrose that is ingested between meals that is most damaging to teeth. Sugar alcohols, such as mannitol, sorbitol, and xylitol, are not cariogenic; xylitol even appears to inhibit carbohydrate metabolism in *S. mutans.* This is why these sugar alcohols are used to sweeten "sugarless" candies and chewing gum.

The best strategies for preventing dental caries are a minimal ingestion of sucrose; brushing, flossing, and professional cleaning to remove plaque; and the use of fluoride. Professional removal of plaque and tartar at regular intervals lessens the progression to periodontal disease.

Periodontal Disease

Even people who avoid tooth decay might, in later years, lose their teeth to **periodontal disease,** a term for a number of conditions characterized by inflammation and degeneration of structures that support the teeth (**Figure 25.5**). The roots of the tooth are protected by a covering of specialized connective tissue called *cementum.* As the gums recede with age or with overly aggressive brushing, the formation of caries on the cementum becomes more common.

Gingivitis

In many cases of periodontal disease, the infection is restricted to the gums, or *gingivae.* This resulting inflammation, called **gingivitis,** is characterized by bleeding of the gums while the teeth are being brushed (see Figure 25.5). This is a condition experienced by at least half of the adult population. It has been shown experimentally that gingivitis will appear in a few weeks if brushing is discontinued and plaque is allowed to accumulate. An assortment of streptococci, actinomycetes, and anaerobic gram-negative bacteria predominate in these infections.

Periodontitis

Gingivitis can progress to a chronic condition called **periodontitis,** an insidious condition that generally causes little discomfort. About

DISEASES IN FOCUS 25.1

Bacterial Diseases of the Mouth

Most adults show signs of gum disease, and about 14% of U.S. adults aged 45 to 54 have a severe case. Use the table below to identify infections that could cause persistent sore, swollen, red, or bleeding gums, as well as tooth pain or sensitivity and bad breath. For the solution, go to MasteringMicrobiology.



This gram-negative rod grown on blood agar accounts for nearly one-quarter of cases.

Disease	Pathogen	Symptoms	Treatment	Prevention
Dental Caries	Primarily *Streptococcus mutans*	Discoloration or hole in tooth enamel	Remove decayed area	Brushing, flossing, reducing dietary sucrose
Periodontal Disease	Various, primarily *Porphyromonas* spp.	Bleeding gums, pus pockets	Remove damaged area; antibiotics	Plaque removal
Acute Necrotizing Ulcerative Gingivitis	*Prevotella intermedia*	Pain chewing, halitosis	Remove damaged area; metronidazole	Brushing, flossing

35% of adults suffer from periodontitis, which is increasing in incidence as more people retain their teeth into old age. The gums are inflamed and bleed easily. Sometimes pus forms in *periodontal pockets* surrounding the teeth (see Figure 25.5). As the infection continues, it progresses toward the root tips. The bone and tissue that support the teeth are destroyed, eventually leading to loosening and loss of the teeth. Numerous bacteria of many different types, primarily *Porphyromonas* (POR-fi-rō-mō-nas) species, are found in these infections; the damage to tissue is done by an inflammatory response to the presence of these bacteria. Periodontitis can be treated surgically by eliminating the periodontal pockets.

Acute necrotizing ulcerative gingivitis, also termed **Vincent's disease** or **trench mouth,** is one of the more common serious mouth infections. The disease causes enough pain to make normal chewing difficult. Foul breath (halitosis) also accompanies the infection. Among the bacteria usually associated with this condition is *Prevotella intermedia* (prev-ō-TEL-lah in-ter-MĒ-dē-ah), averaging up to 24% of the isolates. Because these pathogens are usually anaerobic, treatment with oxidizing agents, debridement, and the administration of metronidazole or antibodies may be temporarily effective. Bacterial diseases of the mouth are summarized in Diseases in Focus 25.1.

CHECK YOUR UNDERSTANDING

- Why are "sugarless" candies and gum, which actually contain sugar alcohols, not considered cariogenic? **25-3**

Bacterial Diseases of the Lower Digestive System

LEARNING OBJECTIVE

25-4 List the causative agents, suspect foods, signs and symptoms, and treatments for staphylococcal food poisoning, shigellosis, salmonellosis, typhoid fever, cholera, gastroenteritis, and peptic ulcer disease.

Diseases of the digestive system are essentially of two types: infections and intoxications.

An **infection** occurs when a pathogen enters the GI tract and multiplies. Microorganisms can penetrate into the intestinal mucosa and grow there, or they can pass through to other systemic organs. **M cells** (microfold cells) translocate antigens and microorganisms to the other side of the epithelium where they can contact lymphoid tissues (Peyer's patches) to initiate an immune response (see page 479, Figure 17.9, and Figure 25.7). Infections of the GI tract are characterized by a delay in the appearance of gastrointestinal disturbance while the pathogen increases in numbers or affects invaded tissue. There is also usually a fever, one of the body's general responses to an infective organism.

Some pathogens cause disease by forming toxins that affect the GI tract. An **intoxication** is caused by the ingestion of such a preformed toxin. Most intoxications, such as that caused by *Staphylococcus aureus,* are characterized by a very sudden appearance (usually in only a few hours) of symptoms of a GI disturbance. Fever is less often one of the symptoms.

Both infections and intoxications often cause *diarrhea,* which most of us have experienced. Severe diarrhea accompanied by blood or mucus is called **dysentery.** Both types of digestive system diseases are also frequently accompanied by *abdominal cramps, nausea,* and *vomiting.* Diarrhea and vomiting are both defensive mechanisms designed to rid the body of harmful material.

The general term **gastroenteritis** is applied to diseases causing inflammation of the stomach and intestinal mucosa. Botulism is a special case of intoxication because the ingestion of the preformed toxin affects the nervous system rather than the GI tract (see Chapter 22, page 614).

In developing countries, diarrhea is a major factor in infant mortality. Approximately one child in every four dies of it before the age of 5. It is estimated that mortality from childhood diarrhea could be halved by *oral rehydration therapy* (replacement of lost fluids and electrolytes). This is usually a solution of sodium chloride, potassium chloride, glucose, and sodium bicarbonate to replace lost fluids and electrolytes. These solutions are sold in the infant supply department of many stores. Recently, the World Health Organization (WHO) has issued a recommendation to replenish losses of zinc during diarrheal episodes with a course of zinc tablets. This has been found to reduce the duration and severity of diarrheal episodes and even help prevent future episodes for 2 or 3 months. Public health departments often determine the incidence of diarrhea in the population by receiving weekly reports on the sales of oral rehydration preparations.

Diseases of the digestive system are often related to food ingestion.

Staphylococcal Food Poisoning (Staphylococcal Enterotoxicosis)

A leading cause of gastroenteritis is **staphylococcal food poisoning,** an intoxication caused by ingesting an enterotoxin produced by *S. aureus.* Staphylococci are comparatively resistant to environmental stresses, as discussed on page 309. They also have a fairly high resistance to heat; vegetative cells can tolerate 60°C for half an hour. Their resistance to drying and radiation helps them survive on skin surfaces. Resistance to high osmotic pressures helps them grow in foods, such as cured ham, in which the high osmotic pressure of salts inhibits the growth of competitors.

S. aureus is often an inhabitant of the nasal passages, from which it contaminates the hands. It's also a frequent cause of skin lesions on the hands. From these sources, it can readily enter food. If the microbes are allowed to incubate in the food, a situation called **temperature abuse,** they reproduce and release enterotoxin into the food. These events, which lead to outbreaks of staphylococcal intoxication, are illustrated in Figure 25.6.

S. aureus produces several toxins that damage tissues or increase the microorganism's virulence. The production of the toxin of serological type A (which is responsible for most cases)

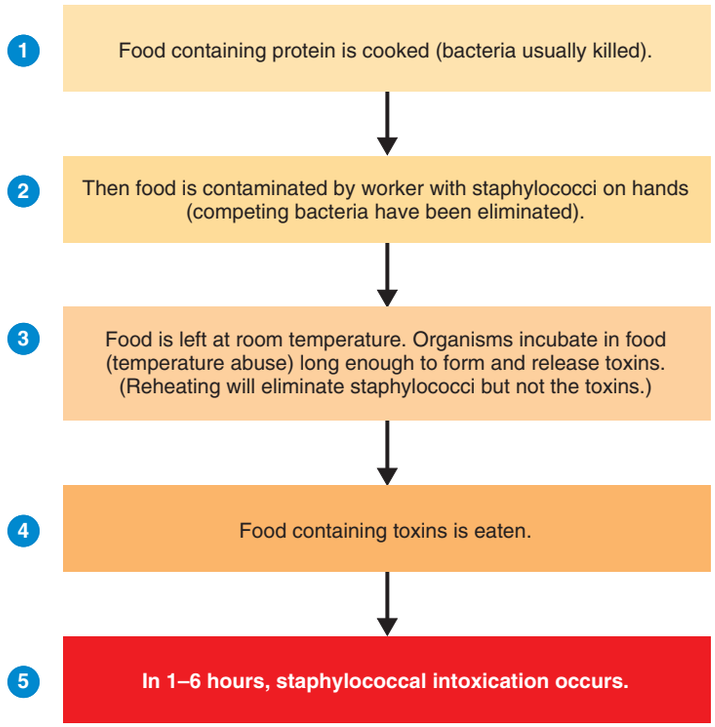


Figure 25.6 The sequence of events in a typical outbreak of staphylococcal food poisoning.

Q How does this differ from foodborne illness caused by a virus?

is often correlated with the production of an enzyme that coagulates blood plasma. Such bacteria are described as *coagulase-positive.* No direct pathogenic effect can be attributed to the enzyme, but it is useful in the tentative identification of types that are likely to be virulent.

Generally, a population of about 1 million bacteria per gram of food will produce enough enterotoxin to cause illness. The growth of the microbe is facilitated if the competing microorganisms in the food have been eliminated—by cooking, for example. It is also more likely to grow if competing bacteria are inhibited by a higher-than-normal osmotic pressure or by a relatively low moisture level. *S. aureus* tends to outgrow most competing bacteria under these conditions.

Custards, cream pies, and ham are examples of high-risk foods. Competing microbes are minimized in custards by the high osmotic pressure of sugar and by cooking. In ham they are inhibited by curing agents, such as salts and preservatives. Because food contamination by human handlers can't be avoided completely, the most reliable method of preventing staphylococcal food poisoning is adequate refrigeration during storage to prevent toxin formation. The toxin itself is heat stable and can survive up to 30 minutes of boiling. Therefore, once the toxin is formed, it is not destroyed when the food is reheated, although the bacteria will be killed.

The mortality rate of staphylococcal food poisoning is almost zero among otherwise healthy people, but it can be significant in weakened individuals, such as residents of nursing homes.

The diagnosis of staphylococcal food poisoning is usually based on the symptoms, particularly the short incubation time characteristic of intoxication. If the food hasn't been reheated so the bacteria are still alive, the pathogen can be recovered and grown. *S. aureus* isolates can be tested by *phage typing,* a method used in tracing the source of the contamination (see Figure 10.13, page 280). These bacteria grow well in 7.5% sodium chloride, so this concentration is often used in media for their selective isolation. Pathogenic staphylococci usually ferment mannitol, produce hemolysins and coagulase, and form golden-yellow colonies. They cause no obvious spoilage when growing in foods. Detecting the toxin in food samples has always been a problem; there may be only 1 to 2 nanograms in 100 g of food. Reliable serological methods have become commercially available only recently.

Shigellosis (Bacillary Dysentery)

Bacterial infections, such as salmonellosis and shigellosis, usually have longer incubation periods (12 hours to 2 weeks) than bacterial intoxications, reflecting the time needed for the microorganism to grow in the host. Bacterial infections are often characterized by some fever, indicating the host's response to the infection.

Shigellosis, also known as **bacillary dysentery** to differentiate it from amebic dysentery (page 735), is a severe form of diarrhea caused by a group of facultatively anaerobic gram-negative rods of the genus *Shigella.* The genus was named for the Japanese microbiologist Kiyoshi Shiga. The bacteria don't have any natural reservoir in animals and spread only from person to person. Outbreaks are most often seen in families, day-care facilities, and similar settings.

There are four species of pathogenic *Shigella: S. sonnei* (SŌN-nē-ē), *S. dysenteriae* (dis-en-TE-rē-ī), *S. flexneri* (FLEKS-ner-ē), and *S. boydii* (BOY-dē-ē). These bacteria are residents only of the intestinal tract of humans, apes, and monkeys. They are closely related to the pathogenic *E. coli.*

The most common species in the United States is *S. sonnei;* it causes a relatively mild dysentery. Many cases of so-called traveler's diarrhea might be mild forms of shigellosis. At the other extreme, infection with *S. dysenteriae* often results in a severe dysentery and prostration. The toxin responsible is unusually virulent and is known as the **Shiga toxin** (see enterohemorrhagic *E. coli,* page 719). *S. dysenteriae,* fortunately, is the least common species of pathogenic *Shigella* in the United States.

The infective dose required to cause disease is small; the bacteria are not much affected by stomach acidity. They proliferate to immense numbers in the small intestine, but the primary site of disease is the large intestine. There, the bacteria attach to certain epithelial cells, M cells (page 479). Membranous cellular ruffles surrounding the cell take the bacterium into the cell. (Similar to invasion by *Salmonella* shown in Figure 15.2). The bacteria multiply in the cell and soon spread to neighboring cells, producing Shiga toxin that destroys tissue (**Figure 25.7**). Dysentery is the result of damage to the intestinal wall.

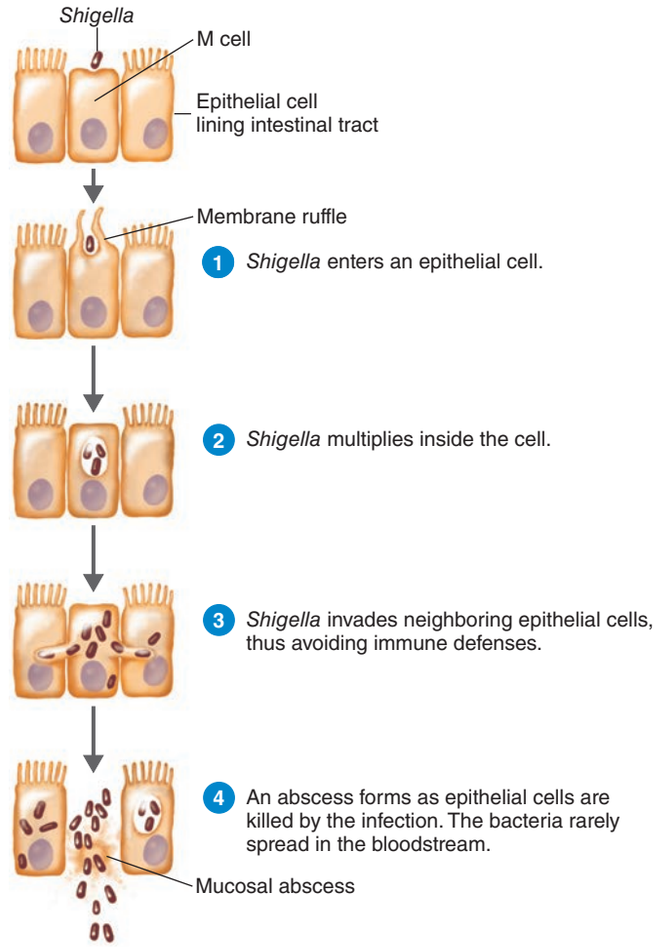


Figure 25.7 Shigellosis. This shows the sequence of infection of the intestinal wall.

Q Why do *Shigella* rarely spread to the bloodstream?

Shigellosis can cause as many as 20 bowel movements in one day. Additional symptoms of infection are abdominal cramps and fever. *Shigella* bacteria rarely invade the bloodstream. Macrophages not only fail to kill *Shigella* bacteria that they phagocytize, but also are killed by them. Diagnosis is usually based on recovery of the microbes from rectal swabs.

The CDC estimates that about 450,000 cases of shigellosis occur annually; most are caused by *S. sonnei* and chiefly affect children under the age of 5. *S. dysenteriae* has a significant mortality rate, however, and the death rate in tropical areas where it's prevalent can be as high as 20%. Some immunity seems to result from recovery, but a satisfactory vaccine has not yet been developed.

In severe cases of shigellosis, antibiotic therapy and oral rehydration are indicated. At present, fluoroquinolones are the antibiotics of choice.

Salmonellosis (*Salmonella* Gastroenteritis)

The *Salmonella* bacteria (named for their discoverer, Daniel Salmon) are gram-negative, facultatively anaerobic, non–endospore-forming rods. Their normal habitat is the intestinal tracts of humans and many animals. All salmonellae are considered pathogenic to some degree, causing **salmonellosis,** or ***Salmonella* gastroenteritis.** Pathogenically, salmonellae are separated into *typhoidal salmonellae* (see typhoid fever, page 716) and the *nontyphoidal salmonellae,* which cause the milder disease of salmonellosis.

The nomenclature of the *Salmonella* microbes differs from the norm. Rather than recognized species, there are more than 2000 serotypes (or serovars), only about 50 of which are isolated with any frequency in the United States. (For a discussion of the nomenclature of the salmonellae, see page 300.) To summarize, many taxonomists consider them to belong to only two species, primarily *Salmonella enterica.* Therefore, you might encounter nomenclature such as *S. enterica* serotype Typhimurium, instead of the conventional name *S. typhimurium.*

The salmonellae first invade the intestinal mucosa and multiply there (see Figure 15.2). Occasionally they manage to pass through the intestinal mucosa at M cells to enter the lymphatic and cardiovascular systems, and from there they may spread and eventually affect many organs (**Figure 25.8**). They replicate readily within macrophages. Salmonellosis has an incubation time of about 12 to 36 hours. There is usually a moderate fever accompanied by nausea, abdominal pain and cramps, and diarrhea. As many as 1 billion salmonellae per gram can be found in an infected person's feces during the acute phase of the illness.

The mortality rate is overall very low, probably less than 1%. However, the death rate is higher in infants and among the very old; death is usually from septic shock. The severity and incubation time can depend on the number of *Salmonella* ingested. Normally, recovery will be complete in a few days, but many patients will continue to shed the organisms in their feces for up to 6 months. Antibiotic therapy isn't useful in treating salmonellosis or, indeed, many diarrheal diseases; treatment consists of oral rehydration therapy.

Salmonellosis is probably greatly underreported. There are an estimated 1.4 million cases and 400 deaths annually (**Figure 25.9**). Meat products are particularly susceptible to contamination by *Salmonella.* The sources of the bacteria are the intestinal tract of many animals. Pet reptiles, such as turtles and iguanas, are also a source; their carriage rate is as high as 90%. In fact, the sale of small turtles (<10 cm) as pets is now prohibited by the FDA because of the risk that children may put them in the mouth. *S. enteritidis* and *S. typhimurium* are especially well adapted to commercial chicken production.

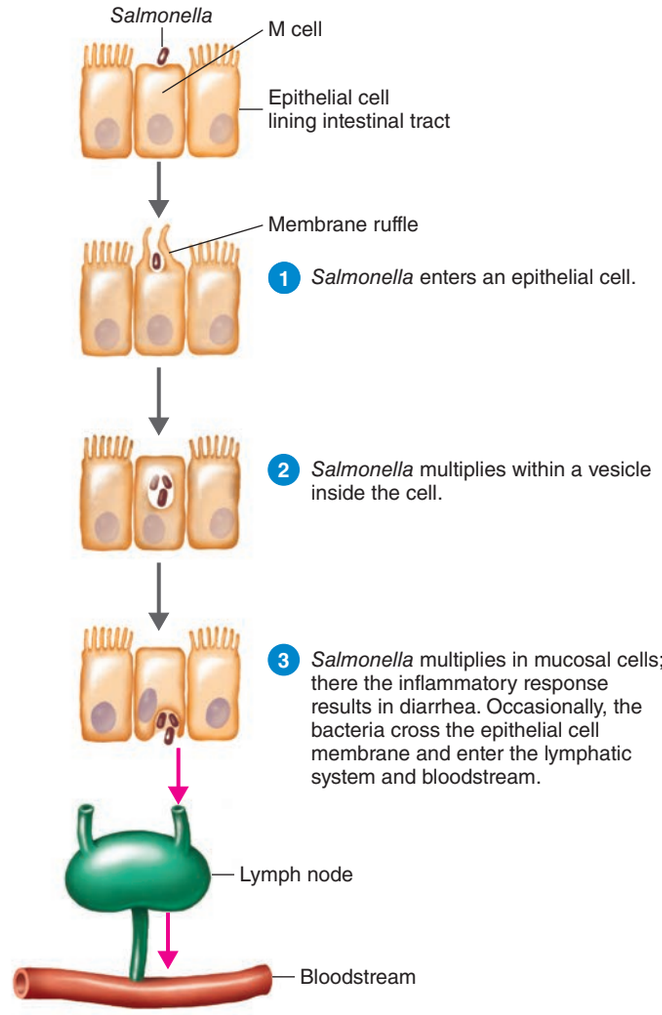


Figure 25.8 Salmonellosis. This shows the sequence of infection of the intestinal wall. Compare with Figure 25.7 showing infection with *Shigella.* Note that invasion of the bloodstream, which happens infrequently, can result in septic shock.

Q Why does salmonellosis have a longer incubation period than a bacterial intoxication?

Hens are highly susceptible to infection, and the bacteria contaminate the eggs. The bacteria have developed the ability to survive in the albumin, which contains natural preservatives such as *lysozyme* (see page 444) and *lactoferrin* (which binds iron the bacteria require). Estimates are that 1 in 20,000 eggs in this country is contaminated by *Salmonella.* Health authorities caution the public to eat only well-cooked eggs. An often unsuspected factor is the presence of inadequately cooked or raw eggs in foods such as hollandaise sauce, cookie batter, and Caesar salad. Fruits have been frequent sources of foodborne illness from ingestion of *Salmonella* (see the box on page 717).

Prevention also depends on good sanitation practices to deter contamination and on proper refrigeration to prevent

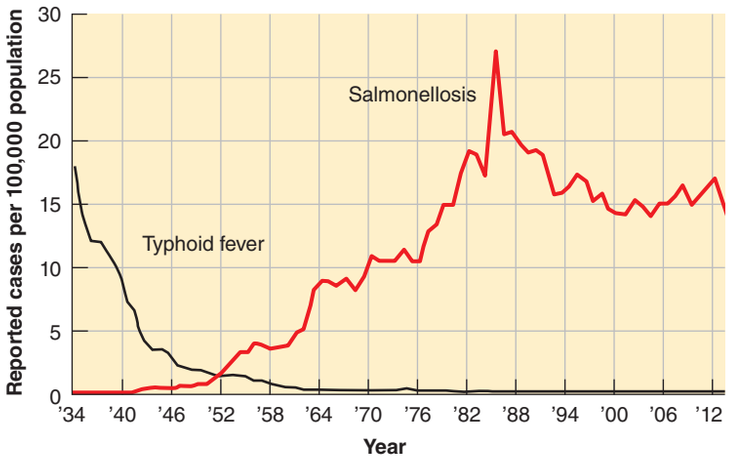


Figure 25.9 The incidence of salmonellosis and typhoid fever. An important factor in comparing the two diseases is that typhoid transmission is almost entirely human-to-human, and salmonellosis is transmitted primarily between animal products and humans.

Source: CDC. *MMWR* 62(52), January 3, 2014.

Can you suggest reasons for the change in prevalence of those two diseases?

increases in bacterial numbers. The microbes are generally destroyed by normal cooking. Chicken, for example, should be cooked at temperatures of 76–82°C and ground beef at 71°C. However, contaminated food can contaminate a surface, such as a cutting board. Then another food subsequently prepared on the board might not be cooked.

Diagnosis usually depends on isolating the pathogen from the patient's stool or from leftover food. Isolation requires specialized selective and differential media; these methods are relatively slow. Also, the small numbers of *Salmonella* generally found in foods present a special problem in detection. The infective dose may be as small as 1000 bacteria. Currently, PCR-based tests are the best for detecting small numbers of *Salmonella* in foods. They require about 5 hours and identify the most common clinical serotypes.

Typhoid Fever

The most virulent serotype of *Salmonella, S. typhi,* causes the bacterial disease **typhoid fever.** Unlike the salmonellae that cause salmonellosis, this pathogen is not found in animals; it's spread only in the feces of other humans. Before the days of proper sewage disposal, water treatment, and food sanitation, typhoid was an extremely common disease. Its incidence has been declining in the United States, whereas that of salmonellosis has been increasing (see Figure 25.9). Typhoid fever is still a frequent cause of death in parts of the world with poor sanitation. Globally, there are an estimated 21 million cases annually, causing tens of thousands of deaths.

Instead of being destroyed by phagocytic cells, *S. typhi* multiply within them and are disseminated into multiple organs, especially the spleen and liver. Eventually, the phagocytic cells lyse and release *S. typhi* into the bloodstream. The time required for this explains why the incubation period of typhoid fever (2 or 3 weeks) is much longer than for salmonellosis (12 to 36 hours). The patient with typhoid fever suffers from a high fever of about 40°C and continual headache. Diarrhea appears only during the second or third week, and the fever then tends to decline. In severe cases, which can be fatal, ulceration and perforation of the intestinal wall can occur. Before antibiotic therapy was available, a mortality rate of 20% was common; with the treatments available today, it is less than 1%.

Substantial numbers of recovered patients, about 1–3%, become *chronic carriers.* They harbor the pathogen in the gallbladder and continue to shed bacteria for several months. A number of such carriers continue to shed the organism indefinitely. The classic example of a typhoid carrier was Mary Mallon, also known as Typhoid Mary. She worked as a cook in New York state in the early part of the twentieth century and was responsible for several outbreaks of typhoid and three deaths. She became well known through the attempts of the state to restrain her from working at her chosen trade.

In recent years there have been about 350 to 400 annual cases of typhoid fever in the United States, of which 70% were acquired during foreign travel. Normally, there are fewer than three deaths each year.

When the antibiotic chloramphenicol was introduced in 1948, typhoid became a treatable disease. Although mostly replaced by safer (but more expensive) antibiotics, it's still used in endemic areas in the world—but might require 250 capsules during a course of treatment. The most effective antityphoidal drugs are quinolones or third-generation cephalosporins. Treatment of the chronic carrier might require weeks of antibiotic therapy. Antibiotic resistance is a frequent problem.

Recovery from typhoid confers lifelong immunity. Vaccines are seldom used in developed countries except for high-risk laboratory or military personnel. The declining effectiveness of antibiotics has renewed interest in vaccination for less developed parts of the world. The vaccine that has long been in use is a killed-organism type, which must be injected and has high rates of side effects. Newer-generation vaccines have become available that are quite safe and can be used in persons 2 years of age or older. One, a subunit vaccine that requires a single injection, confers good protection for at least 3 years. Another, a live attenuated vaccine that can be taken orally in three or four doses, protects well for as long as 7 years.

CHECK YOUR UNDERSTANDING

Why was typhoid fever almost entirely eliminated in developed countries by modern sewage treatment whereas salmonellosis has not been? **25-4**

CLINICAL FOCUS

A Foodborne Infection

As you read through this problem, you'll see questions that epidemiologists ask themselves as they solve a clinical problem. Try to answer each question as an epidemiologist.

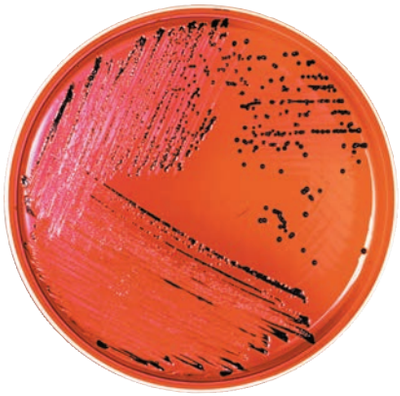
1. On June 29, Joanie, a 36-year-old woman in Ohio is hospitalized with a 3-day history of nausea, vomiting, and diarrhea. She has a temperature of 39.5°C, and she is dehydrated.
   What sample is needed from Joanie to determine the cause of her signs and symptoms?
2. A stool culture grows gram-negative, non–lactose-fermenting bacteria.
   Can you identify the bacteria? (See the photograph.)
3. Joanie is one of 261 culture-confirmed cases in a 24-state outbreak of salmonellosis.
   What information would you try to obtain from these patients?
4. No single restaurant or restaurant chain is associated with the outbreak.
   How will you determine the source of the infection?
5. Epidemiologists conduct a case-control study to compare 53 case-patients with 53 healthy controls from the same geographic locations. All 106 people are asked to complete a questionnaire about foods eaten. (See the table below.)

   Relative risk (RR) is a measure of the probability (risk) that an event will result in disease. The RR must be calculated for each source of exposure.
   Using the 2 × 2 table as a guide, complete the remaining calculations to determine the probable source of the infection.

Exposure	Exposed		Not Exposed		Relative Risk (RR)
	(a) Ill	*(b)* Not Ill	*(c)* Ill	*(d)* Not Ill	
Eggs	47	40	6	13	**1.71**
Chicken	32	20	21	33	
Banana	34	30	19	23	
Milk	42	39	11	14	
Cantaloupe	47	24	6	29	

Relative Risk Calculation using a statistical 2 × 2 contingency table

	Ill	Not Ill	Relative Risk
Ate _____	*(a)*	*(b)*	$(e) = \frac{a}{a + b}$
Did not eat _____	*(c)*	*(d)*	$(f) = \frac{c}{c + d}$
Relative risk =	$\frac{e}{f} =$ _____		= Times more likely to become ill by going to this place



Some *Salmonella* colonies form red colonies with black centers, which allows them to be differentiated from red colonies of *Shigella*.

6. There is a strong association between illness and consumption of cantaloupe. The implicated cantaloupe are packaged at one facility.
   What would you do now?
7. *Salmonella typhimurium* was isolated from surfaces in the packing shed and from cardboard boxes.
   What factors might contribute to cantaloupe as a vehicle of transmission?

The U.S. Food and Drug Administration (FDA) found that the packing area had numerous porous surfaces, such as carpet and wood, that couldn't be cleaned; an accumulation of fruit debris and mud under conveyor belts; and a leaky water line over the conveyor belt. Moreover, the chlorine level of well water used to wash the cantaloupes was not monitored. Researchers are currently investigating the practicality of surface pasteurization of melons.

Source: Adapted from CDC data and inspection report, August 21, 2012.

Cholera

The causative agent of **cholera,** one of the most serious gastrointestinal diseases, is *Vibrio cholerae,* a slightly curved, gram-negative rod with a single polar flagellum (**Figure 25.10**). Cholera bacilli grow in the small intestine and produce an exotoxin, *cholera toxin* (see Chapter 15, page 425), that causes host cells to secrete water and electrolytes, especially potassium. The result is watery stools containing masses of intestinal mucus and epithelial cells—called "rice water stools" from their appearance. As much as 12 to 20 liters (3 to 5 gallons) of fluids can be lost in a day, and the sudden loss of these fluids and electrolytes causes shock, collapse, and often death. The blood, lacking fluids, may become so viscous that vital organs are unable to function properly. Violent vomiting generally also occurs. The microbes are not invasive, and a fever is usually not present. The severity of cholera varies greatly, and the number of subclinical



Figure 25.10 ***Vibrio cholerae,*** **the cause of cholera.** Notice the slightly curved morphology.

Q What are the effects of the sudden loss of fluid and electrolytes during infection with *V. cholerae*?

cases might be several times the number reported. Untreated cases of cholera may have a mortality rate of 50%, although with proper supportive care it is usually less than 1%. The diagnosis is based upon symptoms and culturing of *V. cholerae* from feces.

Cholera bacteria, and other members of the genus *Vibrio* in general, are strongly associated with brackish (salty) waters characteristic of estuaries, although they are also readily spread in contaminated freshwater. They form biofilms and colonize copepods (tiny crustaceans), algae, and other aquatic plants and plankton, which aids their survival. It has even been reported that because of this growth habit, straining contaminated water through folded layers of finely-woven cloth (such as saris worn by Indian women) often removes these attached bacteria and makes the water safe to drink. Under unfavorable conditions, *V. cholerae* may become dormant; the cell shrinks into a nonculturable, spherical state. A favorable change in the environment causes them to revert rapidly to the culturable form. Both forms are infectious.

Although they survive well in their aquatic environment, cholera bacteria are exceptionally sensitive to stomach acids. Persons with impaired stomach acid secretion or who are taking antacids are at higher risk of infection. Normal individuals may require infective doses on the order of 100 million bacteria to cause severe cholera. Recovery from cholera results in an effective immunity, but only to bacterial strains of the same antigenic characteristics. The serogroup O:1 (see the footnote in Chapter 11, page 299), which caused a pandemic in the 1880s, is known as the *classical* strain. A later pandemic was caused by a biotype of O:1 named *El Tor* (for the El Tor quarantine camp for pilgrims to Mecca, where it was first isolated). Until the 1990s it was thought that only *V. cholerae* O:1 caused epidemic cholera, but a widespread epidemic in India and Bangladesh by a new serogroup, O:139, changed this view. There are also nonepidemic strains of *V. cholerae,* non-O:1/O:139, that are only infrequently associated with large-scale outbreaks of cholera. They occasionally cause wound infections or sepsis, especially in people with liver disease or who are immunosuppressed.

In the United States there have been occasional cases of cholera caused by the O:1 serogroup. These have all occurred in the Gulf Coast area, and the pathogen may be endemic in these coastal waters. Outbreaks of cholera in this country are limited by high standards of sanitation. This represents the primary means of control and is important because stools may contain 100 million *V. cholerae* per gram. An example of how this can change quickly was illustrated in 2010, when the Caribbean nation of Haiti experienced an earthquake that seriously damaged much of the water supply and other systems. (See the **Big Picture** on cholera after natural disasters on pages 720–721.) An outbreak of cholera caused several hundred deaths when cholera bacteria of a strain usually found in Asia were introduced from an outside source. Available oral vaccines provide immunity of relatively short duration and only moderate effectiveness.

Treatment often includes the use of antibiotics such as doxycycline, but the most effective therapy is intravenous replacement of the lost fluids and electrolytes. As much as 10% of the patient's body weight within a few hours may be required. Rehydration therapy is so effective that in Bangladesh, for example, where cholera is common, deaths are considered "unusual."

Noncholera Vibrios

At least 11 species of *Vibrio,* in addition to *V. cholerae,* can cause human illness. Most are adapted to life in salty coastal waters. *Vibrio parahaemolyticus* (par′ah-hē-mō-LI-ti-kus) is found in saltwater estuaries in many parts of the world. It is morphologically similar to *V. cholerae* and the most common cause of gastroenteritis by *Vibrio* spp. in humans. The bacterium is present in coastal waters of the continental United States and Hawaii. Raw oysters and crustaceans, such as shrimp and crabs, have been associated with several outbreaks of *gastroenteritis* in the United States in recent years.

Clinical Case

The fecal sample is cultured on sorbitol–MacConkey agar. A sorbitol-negative colony is tested for lactose fermentation. The bacteria produce acid from lactose and do not use citrate as their sole carbon source.

Identify the bacteria by using the identification key in Figure 10.8 on page 276. What does Anna's pediatrician need to know about her history?

These infections are life threatening and require early antibiotic therapy for successful treatment.

Escherichia coli Gastroenteritis

One of the most prolific microorganisms in the human intestinal tract is *Escherichia coli*. Because it's so common and so easily cultivated, microbiologists often regard it as something of a laboratory pet. *E. coli* are normally harmless, but certain strains can be pathogenic. Mobile genetic elements can turn *E. coli* into a highly adapted pathogen causing a range of diseases. Some toxin-secreting pathogenic strains are well adapted to invasion of intestinal epithelial cells, causing *E. coli gastroenteritis*. Other locations, such as the urinary tract, bloodstream, and central nervous system, can also be affected. Eight pathogenic varieties (pathovars) of *E. coli* have been well characterized; we'll discuss five such diarrhea-causing pathovar groups.

Enteropathogenic *E. coli* (EPEC) is a major cause of diarrhea in developing countries and is potentially fatal in infants. As the bacteria attach to the intestinal wall, they eliminate surrounding microvilli and stimulate host-cell actin to form pedestals beneath their site of attachment (**Figure 25.11**). EPEC bacteria secrete a number of effector proteins that are translocated into host cells, some contributing to diarrhea.

Enteroinvasive *E. coli* (EIEC) is generally agreed to be almost synonymous with *Shigella*—it has the same pathogenic mechanisms. EIEC gain access to the submucosa of the intestinal tract through M cells (see Figure 25.7) in the same manner as *Shigella*. This invasion results in inflammation, fever, and a *Shigella*-like dysentery.

Enteroaggregative *E. coli* (EAEC) is a group of coliforms found only in humans. They are named for their growth habit, in which the bacteria cause a "stacked-brick" configuration on tissue culture cells. EAEC are not invasive but produce an enterotoxin causing a watery diarrhea.

In recent years, strains of **enterohemorrhagic *E. coli* (EHEC)** have caused several outbreaks of serious disease in the United States. The primary virulence factor in these bacteria is a Shiga-like toxin. Shiga toxins are a family of toxins that are closely related. Some *E. coli* strains that produce Shiga-like toxins are termed Shiga-toxin-producing *E. coli* (STEC). True Shiga toxin is produced only by *Shigella dysenteriae*. Most outbreaks are due to EHEC serotype O157:H7. Other lesser known strains include O121 and O104:H21. (Refer to page 299 for an explanation of this numerical nomenclature.) Because the toxin is released upon the cell's lysis, antibiotic therapy can worsen the attack by causing the release of more toxin.

Cattle, which are not affected by the pathogen, are the main reservoir; infections are spread by contaminated food or water. Currently, 2–3% of domestic cattle carry STEC, which contaminate the carcass at slaughter. There are requirements for testing ground meats for the presence of this strain of *E. coli,* especially if intended for export. Leafy vegetables may also be contaminated, sometimes by runoff from feedlots. Ingested food is not the only infection source; some cases have been associated with children's visits to farms or petting zoos. The infective dose is estimated to be very small, probably fewer than 100 bacteria.



Figure 25.11 Pedestal formation by Enterohemorrhagic *E. coli* (EHEC) O157:H7. As EHEC bacteria (purple) adhere to the epithelial wall, they destroy the surface microvilli and cause the formation of a pedestal-like projection (yellow) on which they rest. The function of these actin-rich structures is unclear, but they may facilitate the bacteria's spread to adjacent cells.

Q Is adhesion a factor in the pathogenicity of a microbe?

In humans, the Shiga toxins often cause only self-limiting diarrhea, but in about 6% of infected people, it produces an inflammation of the colon (the last part of the large intestine, ending just above the rectum) involving profuse bleeding, called *hemorrhagic colitis*. Unlike *Shigella,* these *E. coli* bacteria don't invade the intestinal wall (see Figure 25.7), but rather release the toxin into the intestinal lumen (space).

Another dangerous complication is *hemolytic uremic syndrome (HUS)*. Characterized by blood in the urine, often leading to kidney failure, HUS occurs when the kidneys are affected by the toxin. Some 5–10% of young children who have been infected progress to this stage, which has a mortality rate of about 5%. Management of these patients primarily involves intravenous rehydration and careful monitoring of serum electrolytes. Some survivors of HUS may require kidney dialysis or even transplants. An estimated 200 to 500 deaths occur annually.

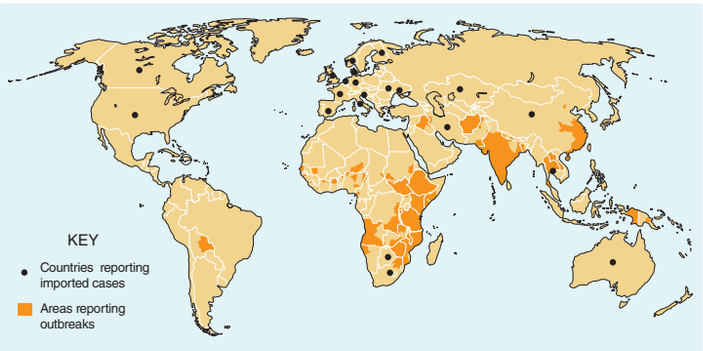
Because of the attention this pathogen has attracted, researchers have been working, with some success, to develop rapid methods of detecting its presence in food without the need for time-consuming culturing methods. It's recommended that public health laboratories test routinely for STEC. A standard

BIG PICTURE

Cholera After Natural Disasters

Cholera is one of the most feared diseases that occurs after natural disasters. Accurate tracking of the true causes of these epidemics can lead to better treatment and prevention.

Many people assume that the greatest source of disease that breaks out after natural disasters is dead bodies. However, studies show that displacement of the survivors and disruption of access to safe water are the biggest contributors. Cholera is a diarrheal disease that can increase when sanitation and modern sewage disposal systems are compromised. In 1991, an outbreak in Peru caused over 1 million cases and 10,000 deaths. An epidemic of over 16,000 cases occurred after flooding in West Bengal in 1998. In 2004, 17,000 cases of diarrheal disease, including cholera, struck Bangladesh after severe floods. And in 2010, a cholera epidemic affected over 600,000 people in earthquake-ravaged Haiti, resulting in over 7000 deaths.



***V. cholerae* nearly identical to a strain circulating in Nepal infected and killed thousands with cholera in Haiti (circled area on map) starting in 2010.** *Source:* World Health Organization.



People in Port-Au-Prince, Haiti, line up for clean drinking water after the 2010 earthquake.



***Vibrio cholerae* bacteria**

What Caused Cholera to Return to Haiti after the 2010 Earthquake?

Cholera's appearance in Haiti after its major earthquake was something of a mystery. No outbreaks had occurred in the region for about a century. The epidemic also occurred nearly 10 months after the earthquake, well into relief and rebuilding efforts. Using gel electrophoresis and whole-genome sequence typing, epidemiologists determined that the *Vibrio cholerae* responsible for most cases was an Asian strain nearly identical to one circulating in Nepal the same year Haiti's outbreak began. It is hypothesized that infected Nepalese soldiers who were part of a United Nations (U.N.) peacekeeping force brought the pathogen to Haiti, where a deficient septic system at the Nepalese base allowed a stream to be contaminated with base sewage. The stream flows into a river many Haitians use for drinking water. The initial outbreak developed among people who drank water downstream from the base.

News of the possible source of the epidemic sparked widespread anger and accusations in Haiti. Although numerous studies—including ones commissioned by the U.N. itself—agree that the peacekeeper troops were the likely source of *V. cholerae,* so far the U.N. claims diplomatic immunity for the incident, meaning that the organization cannot be prosecuted for related damages. Despite that, in 2013 activists attempted to bring a lawsuit against the U.N., citing the huge cost of cholera to victims and alleging that the U.N. behaved negligently.

Disaster and Disease—Searching for Solutions

Strategies for Disaster Preparedness

- **Oral Rehydration Solutions** Cholera's mortality rate is significantly reduced by treating victims with oral rehydration solutions made from salt, sugar, and water. Since the 1970s, this therapy is estimated to have saved over 40 million lives. Teaching global citizens how to prepare this life-saving solution can prevent many deaths from diarrheal diseases after disasters. At health care facilities, cholera cots, specially designed beds, are also used to collect and measure feces lost during infection so the same amount of fluid can be replaced in the patient.
- **Stockpiling Vaccines** Disaster preparedness experts have learned from the Haiti earthquake and subsequent cholera outbreak that stockpiling vaccines, when possible, can help to prevent future outbreaks like this one. One study on oral cholera vaccine in the aftermath of the Haiti earthquake demonstrated that vaccinating even half of an area's population made outbreaks less likely by providing herd immunity to the community at large.

Oral vaccine stockpiles, when quickly dispensed, can help curb outbreaks before they become widespread. According to the World Health Organization, about 3–5 million cholera cases occur annually, with 100,000–120,000 deaths due to fluid loss.

The Ultimate Solution

While oral rehydration therapy and vaccines can be helpful once a cholera outbreak begins, the ultimate solution to a cholera epidemic is to engineer proper sanitation, a goal that is more long-range and expensive. The World Health Organization estimates that over 760 million people lack access to safe water and 2.5 billion people lack proper sanitation—and that's within their daily lives, not due to disruptions in normal sanitation after a disaster event. Many public and private agencies are developing programs to tackle this large goal. For example, the CDC's WASH (Water, Sanitation and Hygiene) Program promotes safe household water storage techniques, handwashing interventions, and training of community health workers. Their efforts have resulted in a 25% decrease in childhood diarrheal infections within four Central American countries, and 50% fewer diarrheal infections in children receiving weekly handwashing lessons.

KEY CONCEPTS

- While natural disasters do not automatically cause disease outbreaks, damage to water and sanitation infrastructure can increase the risk of diarrheal diseases such as cholera. **(See Chapter 27, "Water Treatment" page 784 and "Sewage Treatment" page 785.)**
- Vaccination of a majority of the population can lead to herd immunity that protects the unvaccinated within that community. **(See Chapter 18, "Principles and Effects of Vaccination," pages 493–500.)**
- Tracking the genomics of pathogens has become a mainstay of monitoring, preventing, and controlling infectious disease outbreaks. **(See Chapter 9, "Forensic Microbiology," pages 254–256.)**



A health educator demonstrating how to make an oral rehydration solution from water, salt, and sugar in Thiruvananthapuram, India. Treating cholera victims with this solution can significantly reduce mortality.

method is to use media that differentiate these bacteria by their inability to ferment sorbitol. Any sorbitol-negative colonies should subsequently be tested by a process called *pulsed-field gel electrophoresis (PFGE),* a DNA fingerprinting technique that subtypes bacteria. The data are entered into a national PulseNet database so that epidemiological information can be compared.

Vaccines that greatly lower the numbers of O157: H7 bacteria in cattle have been licensed, but it is uncertain whether they will find widespread use.

A pathogenic group of *E. coli* called **enterotoxigenic *E. coli* (ETEC)** secretes enterotoxins that cause diarrhea. The illness is frequently fatal for children under 5. One of the enterotoxins ETEC produces resembles the cholera toxin in function. ETEC bacteria are not invasive and remain in the intestinal lumen.

Traveler's Diarrhea

It has long been observed that travel broadens the mind and loosens the bowels, leading to the common name of **traveler's diarrhea.** The most common bacterial cause is ETEC; the second most frequent isolate is EAEC. Traveler's diarrhea can also be caused by other gastrointestinal pathogens, such as *Salmonella, Shigella,* and *Campylobacter*—as well as by various unidentified bacterial pathogens, viruses, and protozoan parasites. In fact, in most cases the causative agent is never identified, and chemotherapy is not attempted. Once contracted, the best treatment is the usual oral rehydration recommended for all diarrhea. In severe cases, antimicrobial drugs may be necessary. Prescribed antibiotics may provide some protection; another option is to take bismuth-containing preparations, such as Pepto-Bismol, but the best advice in risky areas is to prevent infection.

Campylobacter Gastroenteritis

Campylobacter are gram-negative, microaerophilic, spirally curved bacteria that have emerged as the leading cause of foodborne illness in the United States. They adapt well to the intestinal environment of animal hosts, especially poultry. Culturing *Campylobacter* requires conditions of low oxygen and high carbon dioxide developed in special apparatus. The bacteria's optimum growth temperature of about 42°C approximates that of their animal hosts, but the bacteria do not replicate in food. Almost all retail chicken is contaminated with *Campylobacter.* Nearly 60% of cattle excrete the organism in feces and milk, but retail red meats are less likely to be contaminated.

There are more than an estimated 2 million cases of ***Campylobacter* gastroenteritis** in the United States annually, usually caused by *C. jejuni.* The infective dose is fewer than a thousand bacteria. Clinically, it is characterized by fever, cramping abdominal pain, and diarrhea or dysentery. Normally, recovery follows within a week.

An unusual complication of campylobacterial infection is that it is linked, in about 1 in 1000 cases, to the neurological disease *Guillain-Barré syndrome,* a temporary paralysis. Apparently, a surface molecule of the bacteria resembles a lipid component of nervous tissue and provokes an autoimmune attack.

Helicobacter Peptic Ulcer Disease

In 1982, a physician in Australia cultured a spiral-shaped, microaerophilic bacterium observed in the biopsied tissue of stomach ulcer patients. Now named *Helicobacter pylori,* it is accepted that this microbe is responsible for most cases of **peptic ulcer disease.** This syndrome includes gastric and duodenal ulcers. (The duodenum is the first few inches of the small intestine.) About 30–50% of the population in the developed world become infected; the infection rate is higher elsewhere. Only about 15% of those infected develop ulcers, so certain host factors are probably involved. For example, people with type O blood are more susceptible, which is also true of cholera. (See page 522.) *H. pylori* is also designated as a carcinogenic bacterium. Gastric cancer develops in about 3% of people infected with these bacteria.

The stomach mucosa contains cells that secrete gastric juice containing proteolytic enzymes and hydrochloric acid that activates these enzymes. Other specialized cells produce a layer of mucus that protects the stomach itself from digestion. If this defense is disrupted, an inflammation of the stomach (gastritis) results. This inflammation can then progress to an ulcerated area (**Figure 25.12**). Through an interesting adaptation, *H. pylori* can grow in the highly acidic environment of the stomach, which is lethal for most microorganisms. *H. pylori* produces large amounts of an especially efficient urease, an enzyme that converts urea to the alkaline compound ammonia, resulting in a locally high pH in the area of growth.

The eradication of *H. pylori* with antimicrobial drugs usually leads to the disappearance of peptic ulcers. Several antibiotics, usually administered in combination, have proven effective. Bismuth subsalicylate (Pepto-Bismol) is also effective and is often part of the drug regimen. When the bacteria are successfully eliminated, the recurrence rate of the ulcer is only about 2–4% a year. Reinfection can result from many environmental sources but is less likely in areas with high standards of sanitation; in fact, there is some evidence that infection by *H. pylori* is slowly disappearing in developed countries.

The most reliable diagnostic test requires a biopsy of tissue and culture of the organism. An interesting diagnostic approach is the urea breath test. The patient swallows radioactively labeled urea; if the test is positive, CO_2 labeled with radioactivity can be detected in the breath within about 30 minutes. This test is most useful for determining the effectiveness of chemotherapy because a positive test is an indication of live *H. pylori.* Diagnostic tests of stools to detect antigens (not antibodies) for *H. pylori* are suitable for follow-up tests following therapy. They are the noninvasive test of choice, especially for children. Serological tests to detect antibodies are inexpensive but not useful in determining eradication.

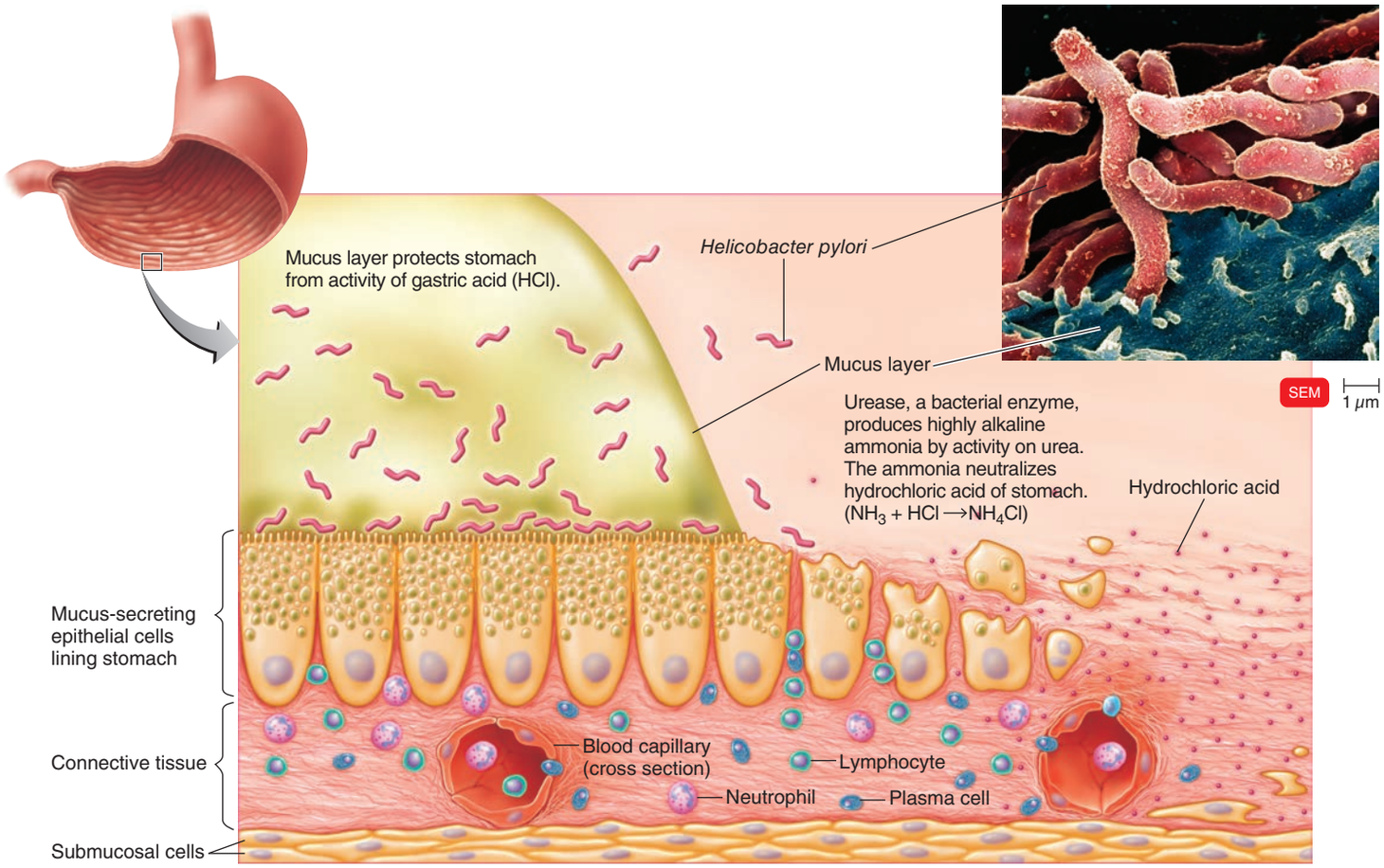


Figure 25.12 *Helicobacter pylori* infection, leading to ulceration of the stomach wall. To survive in the acidic environment of the stomach, *H. pylori* bacteria must neutralize the gastric acid, hydrochloric acid (HCl). They do this by producing large amounts of the enzyme urease. Urea, which is normally secreted into the stomach, is converted into carbon dioxide and ammonia [$(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3$]. The ammonia neutralizes the gastric HCl ($NH_3 + HCl \rightarrow NH_4Cl$).

Q How can ammonia be used to diagnose *Helicobacter* infection?

Yersinia Gastroenteritis

Other enteric pathogens being identified with increasing frequency are *Yersinia enterocolitica* (en′ter-ō-kōl-IT-ik-ah) and *Y. pseudotuberculosis* (soo′dō-too′ber-kū-LŌ-sis). These gram-negative bacteria are intestinal inhabitants of many domestic animals and are often transmitted in meat and milk. Both microbes are distinctive in their ability to grow at refrigerator temperatures of 4°C. This ability increases their numbers in stored refrigerated blood, to the extent that their endotoxins can result in shock to the blood recipient. *Yersinia* has occasionally been the cause of severe reactions when it contaminates transfused blood.

These pathogens cause ***Yersinia* gastroenteritis,** or **yersiniosis.** The symptoms are diarrhea, fever, headache, and abdominal pain. The pain is often severe enough to cause a misdiagnosis of appendicitis. Diagnosis requires culturing the organism, which can then be evaluated by serological tests. Adults suffering from yersiniosis usually recover in 1 or 2 weeks; children may take longer. Treatment with antibiotics and oral rehydration may be helpful.

Clostridium perfringens Gastroenteritis

One of the more common, if underrecognized, forms of food poisoning in the United States is caused by *Clostridium perfringens,* a large, gram-positive, endospore-forming, obligately anaerobic rod. This bacterium is also responsible for human gas gangrene (see Chapter 23, page 646).

Most outbreaks of ***Clostridium perfringens* gastroenteritis** are associated with meats or meat stews contaminated with intestinal contents of the animal during slaughter. Such foods meet the pathogen's nutritional requirement for amino acids, and when the meats are cooked, the oxygen level is lowered

enough for clostridial growth. The endospores survive most routine heatings, and the generation time of the vegetative bacterium is less than 20 minutes under ideal conditions. Large populations can therefore build up rapidly when foods are being held for serving or when inadequate refrigeration leads to slow cooling.

The microbe grows in the intestinal tract and produces an exotoxin that causes the typical symptoms of abdominal pain and diarrhea. Most cases are mild and self-limiting and probably are never clinically diagnosed. If treatment is required, oral rehydration is recommended. The symptoms usually appear 8 to 12 hours after ingestion. Diagnosis is usually based on isolating and identifying the pathogen in stool samples.

Clostridium difficile–Associated Diarrhea

***Clostridium difficile*–associated diarrhea** is a disease condition that has appeared in recent decades and has been described as being responsible for more deaths than all other intestinal infections combined. *C. difficile* is a gram-positive, endospore-forming anaerobe found in the stool of many healthy adults. The exotoxins it produces cause a disease that manifests itself in symptoms ranging from a mild case of diarrhea to life-threatening colitis (inflammation of the colon). The colitis can result in ulceration, and possible perforation, of the intestinal wall. The disease is usually precipitated by the extended use of antibiotics, especially fluoroquinolones. The elimination of most competing intestinal bacteria permits rapid proliferation of the toxin-producing *C. difficile*. Occurring mostly as a healthcare-associated disease in hospitals and nursing homes, *C. difficile*–associated diarrhea is now also affecting the community at large. Outbreaks have occurred in day-care centers, and caregivers have been known to acquire it from patients. The mortality rate is highest in elderly patients. A newer strain, known as BI/NAP1/027, is capable of producing much more exotoxin and is occurring at near-epidemic rates.

Bacillus cereus Gastroenteritis

Bacillus cereus (SEER-ē-us) is a large, gram-positive, endospore-forming bacterium that is very common in soil and vegetation and is generally considered harmless. It has, however, been identified as the cause of outbreaks of foodborne illness. Heating the food does not always kill the spores, which germinate as the food cools. Because competing microbes have been eliminated in the cooked food, *B. cereus* grows rapidly and produces toxins. Rice dishes served in Asian restaurants seem especially susceptible.

Some cases of ***Bacillus cereus* gastroenteritis** resemble *C. perfringens* intoxications and are almost entirely diarrheal in nature (usually appearing 8 to 16 hours after ingestion). Other episodes involve nausea and vomiting (usually 2 to 5 hours after ingestion). It's suspected that different toxins are involved in producing the differing symptoms. Both forms of the disease are self-limiting. The diseases can be differentiated by isolating at least 10^5 *B. cereus* per gram of suspected food.

Bacterial diseases of the GI tract are summarized in Diseases in Focus 25.2.

Clinical Case

The bacteria are identified as *Escherichia coli* O157. The laboratory then uses DNA fingerprinting to identify the strain of *E. coli* as STEC O157. The state health department, which has been notified about the STEC O157 isolate by Anna's pediatrician, makes further inquiries and traces contacts. Mrs. Abramovic is interviewed with a standard questionnaire that focuses on details of travel history, food history, and exposure to animals. According to Mrs. Abramovic, Anna did not consume high-risk foods, such as undercooked ground beef and unpasteurized milk, but her birthday party had been held at a petting zoo the weekend before the onset of her symptoms. Anna had petted the animals and had played on the ground. No other cases occurred in the household or among close contacts.

What should the health department do next?

708 718 724 731 739

Viral Diseases of the Digestive System

LEARNING OBJECTIVES

- **25-5** List the causative agents, modes of transmission, sites of infection, and symptoms for mumps.
- **25-6** Differentiate hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E.
- **25-7** List the causative agents, mode of transmission, and symptoms of viral gastroenteritis.

Although viruses don't reproduce within the contents of the digestive system like bacteria, they invade many organs associated with the system.

Mumps

The targets of the mumps virus, the parotid glands, are located just below and in front of the ears (see Figure 25.1). Because the parotids are one of the three pairs of salivary glands of the digestive system, it is appropriate to include a discussion of mumps in this chapter.

Mumps typically begins with painful swelling of one or both parotid glands 16 to 18 days after exposure to the virus

(**Figure 25.13**). The virus is transmitted in saliva and respiratory secretions, and its portal of entry is the respiratory tract. An infected person is most infective to others during the first 48 hours before clinical symptoms appear. Once the viruses have begun to multiply in the respiratory tract and local lymph nodes in the neck, they reach the salivary glands via the blood. Viremia (the presence of virus in the blood) begins several days before the onset of mumps symptoms and before the virus appears in saliva. The virus is present in the blood and saliva for 3 to 5 days after the onset of the disease and in the urine after about 10 days.

Mumps is characterized by inflammation and swelling of the parotid glands, fever, and pain during swallowing. About 4 to 7 days after the onset of symptoms, the testes can become inflamed, a condition called *orchitis*. This happens in about 20–40% of men past puberty; sterility is a possible but rare consequence. Other possible complications include meningitis, inflammation of the ovaries, and pancreatitis.

An effective attenuated live vaccine is available and is often administered as part of the trivalent measles, mumps, rubella (MMR) vaccine. Second attacks are rare, and cases involving only one parotid gland or subclinical cases (about 15–20% of those infected), are as effective as bilateral mumps in conferring immunity.

If confirmation of the diagnosis (which usually is based only on symptoms) is desired, the virus can be isolated by embryonated egg or cell culture techniques and identified by ELISA tests.

CHECK YOUR UNDERSTANDING

Why is mumps included with the diseases of the digestive system? **25-5**

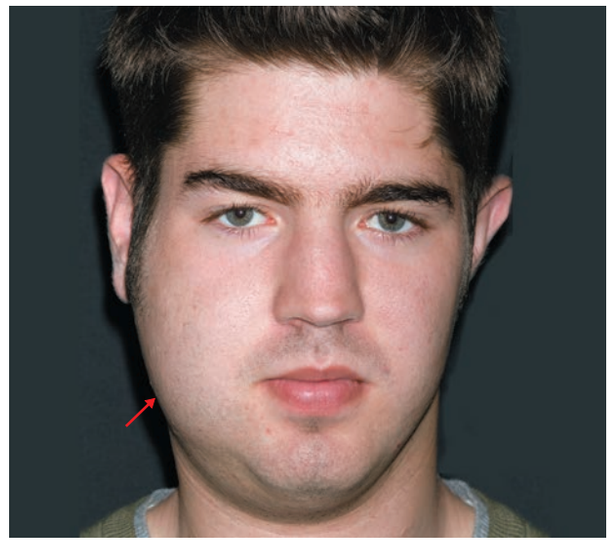


Figure 25.13 A case of mumps. This patient shows the typical swelling of mumps.

How is the mumps virus transmitted?

Hepatitis

Hepatitis is an inflammation of the liver. At least five different viruses cause hepatitis, and probably more remain to be discovered or become better known. Hepatitis is an occasional result of infections by other viruses such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV). Drug and chemical toxicity can also cause acute hepatitis that is clinically identical to viral hepatitis. The characteristics of the various forms of viral hepatitis are summarized in Diseases in Focus 25.3 on page 728.

Hepatitis A

The *hepatitis A virus (HAV)* is the causative agent of **hepatitis A.** The virus contains single-stranded RNA and lacks an envelope. It can be grown in cell culture.

After a typical entrance via the oral route, HAV multiplies in the epithelial lining of the intestinal tract. Viremia eventually occurs, and the virus spreads to the liver, kidneys, and spleen. The virus is shed in the feces and can also be detected in the blood and urine. The amount of virus excreted is greatest before symptoms appear and then declines rapidly. Therefore, a food handler responsible for spreading the virus might not appear to be ill at the time. The virus can probably survive for several days on such surfaces as cutting boards. HAV is resistant to chlorine disinfectants at concentrations ordinarily used in water, a characteristic that enhances fecal contamination of food or drink. Mollusks, such as oysters, that live in contaminated waters are also a source of infection.

At least 50% of infections with HAV are subclinical, especially in children. In clinical cases, the initial symptoms are anorexia (loss of appetite), malaise, nausea, diarrhea, abdominal discomfort, fever, and chills. These symptoms are more likely to appear in adults; they last 2 to 21 days, and the mortality rate is low. Nationwide epidemics occur about every 10 years, mostly in people under 14. In some cases, there is also jaundice (signs are yellowing of the skin and the whites of the eyes) and the dark urine typical of liver infections. In these cases, the liver becomes tender and enlarged.

There is no chronic form of hepatitis A, and the virus is usually shed only during the acute stage of disease. The incubation time averages 4 weeks and ranges from 2 to 6 weeks, making epidemiological studies for the source of infections difficult. There are no animal reservoirs.

In the United States, the percentage of the population that becomes infected with HAV is much higher among lower socioeconomic groups (72–88%) than among middle and upper socioeconomic groups (18–30%). The 30,000 or more cases reported in the United States each year represent only a fraction of the actual number.

Acute disease is diagnosed by the detection of IgM anti-HAV because these antibodies appear about 4 weeks after infection and disappear about 3 to 4 months after infection. Recovery results in lifelong immunity.

DISEASES IN FOCUS 25.2

Bacterial Diseases of the Lower Digestive System

An 8-year-old boy has diarrhea, chills, fever (39.3°C), abdominal cramps, and vomiting for 3 days. The next month, his 12-year-old brother experiences the same symptoms. Two weeks before the first patient became ill, the family had purchased a small (<10 cm) red-eared slider turtle at a flea market. Use the table below and the information on pages 712–716 to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Red-eared slider pets should be >10 cm (4 in.), large enough that children can't put the turtles in their mouths.

Disease	Pathogen	Symptoms	Intoxication/ Infection	Diagnostic Test	Treatment
Staphylococcal Food Poisoning	*Staphylococcus aureus*	Nausea, vomiting, and diarrhea	Intoxication (enterotoxin)	Phage typing	None
Shigellosis (bacillary dysentery)	*Shigella* spp.	Tissue damage and dysentery	Infection (endotoxin and Shiga toxin, exotoxin)	Isolation of bacteria on selective media	Quinolones
Salmonellosis	*Salmonella enterica*	Nausea and diarrhea	Infection (endotoxin)	Isolation of bacteria on selective media, serotyping	Oral rehydration
Typhoid Fever	*Salmonella typhi*	High fever, significant mortality	Infection (endotoxin)	Isolation of bacteria on selective media, serotyping	Quinolones; cephalosporins
Cholera	*Vibrio cholerae* O:1 and O:139	Diarrhea with large water loss	Infection (exotoxin)	Isolation of bacteria on selective media	Rehydration; doxycycline
***Vibrio parahaemolyticus* Gastroenteritis**	*V. parahaemolyticus*	Cholera-like diarrhea, but generally milder	Infection (enterotoxin)	Isolation of bacteria on 2–4% NaCl	Rehydration; antibiotics
***Escherichia coli* Gastroenteritis**	EPEC, EIEC, EAEC, ETEC	Watery diarrhea	Infection (exotoxins)	Isolation on selective media, DNA fingerprinting	Oral rehydration
Shiga Toxin–Producing Enterohemorrhagic *E. coli*	*E. coli* O157:H7	*Shigella*-like dysentery; hemorrhagic colitis, HUS	Infection, Shiga toxin (exotoxin)	Isolation, sorbitol fermentation test, DNA fingerprinting	Intravenous rehydration, serum electrolyte monitoring
***Campylobacter* Gastroenteritis**	*Campylobacter jejuni*	Fever, abdominal pain, diarrhea	Infection	Isolation in low O_2, high CO_2	None
***Helicobacter* Peptic Ulcer Disease**	*Helicobacter pylori*	Peptic ulcers	Infection	Urea breath test, bacterial culture	Antimicrobial drugs
***Yersinia* Gastroenteritis**	*Yersinia enterocolitica*	Abdominal pain and diarrhea, usually mild; may be confused with appendicitis	Infection (endotoxin)	Culture, serotyping	Oral rehydration
***Clostridium perfringens* Gastroenteritis**	*Clostridium perfringens*	Usually limited to diarrhea	Infection (exotoxin)	Isolation of bacteria	Oral rehydration
***C. difficile*–Associated Diarrhea**	*Clostridium difficile*	Mild diarrhea to colitis; 1–2.5% mortality	Infection (exotoxin)	Cytotoxin assay	Metronidazole, vancomycin
***Bacillus cereus* Gastroenteritis**	*B. cereus*	May take form of diarrhea, nausea, vomiting	Intoxication	Isolation of $\geq 10^5$ *B. cereus*/g food	None

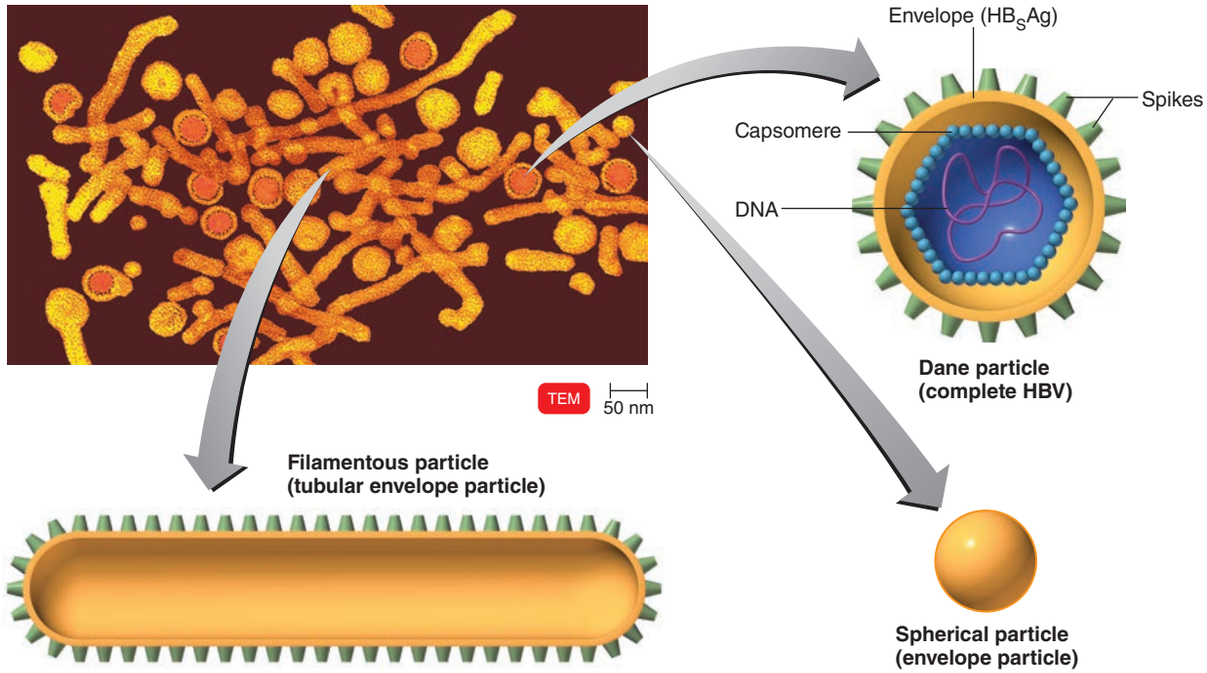


Figure 25.14 Hepatitis B virus (HBV). The micrograph and illustrations depict the distinct types of HBV particles discussed in the text.

Q What are other causes of viral hepatitis?

No specific treatment for the disease exists, but people at risk of exposure or who have been exposed to hepatitis A can be given immune globulin, which provides protection for several months. Inactivated vaccines are now available and are recommended for travelers to areas of endemic disease and for high-risk groups, such as homosexual men and injecting drug users (IDUs). HAV vaccination is now part of the recommended childhood vaccination schedule.

Hepatitis B

Hepatitis B is caused by the *hepatitis B virus (HBV).* HBV and HAV are completely different viruses: HBV is larger, its genome is double-stranded DNA, and it is enveloped. HBV is a unique DNA virus; instead of replicating its DNA directly, it passes through an intermediate RNA stage resembling a retrovirus. Because HBV has often been transmitted by blood transfusions, this virus has been intensely studied to determine how to identify contaminated blood.

The serum from patients with hepatitis B contains three distinct particles (**Figure 25.14**). The largest is the complete virion; it's infectious and capable of replicating. It's often referred to as a *Dane particle,* after the virologist who first observed it. There are also smaller *spherical particles,* about half the size of a complete virion, and *filamentous particles,* which are tubular particles similar in diameter to the spherical particles but about ten times as long. The spherical and filamentous particles are unassembled components of the virion without nucleic acids; assembly is evidently not very efficient, and large numbers of these unassembled components accumulate. Fortunately, these numerous unassembled particles contain *hepatitis B surface antigen (HB_sAg),* which can be detected with antibodies to them. Such antibody tests make convenient screening of blood for HBV possible.

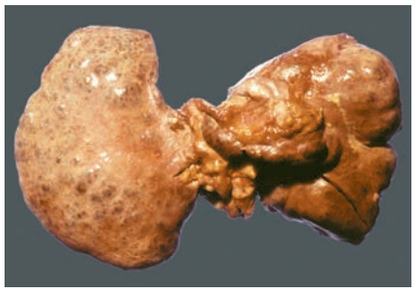
Health care workers and others who are in daily contact with blood have a considerably higher incidence of hepatitis B than members of the general population. It's estimated that thousands of health care workers become infected each year in the United States. Federal regulations require that employees exposed to blood be offered free vaccinations by their employers. There have also been instances of transmission to patients by surgeons and dentists. It is safest to use disposable syringes and needles for each patient. Intravenous drug users often share syringes and needles and fail to sterilize them properly; as a consequence, they also have a high incidence of hepatitis B. Blood may contain up to a billion viruses per milliliter. Therefore, it isn't surprising that the virus is also present in many body fluids, such as saliva, breast milk, and semen, but not in blood-free feces or urine. Transmission by semen donated for artificial insemination has been documented, and semen has been implicated in transmission between heterosexuals with multiple partners and in male homosexuals. Precautions taken to prevent HIV transmission have also had an effect on the incidence of HBV infections. A mother who is positive for HB_sAg, especially if she is a chronic carrier, may transmit the disease

DISEASES IN FOCUS 25.3

Characteristics of Viral Hepatitis



Healthy liver.



Liver damaged by hepatitis C.

Hepatitis is an inflammation of the liver. Chronic hepatitis may be asymptomatic, or there may be evidence of liver disease (including cirrhosis or liver cancer). Hepatitis can be caused by a variety of viruses, alcohol, or drugs; however, it is most often caused by one of the following viruses. Use the table below to determine which virus is the most likely cause of this infection: After eating at one restaurant, 355 people are diagnosed with the same hepatitis virus. For the solution, go to MasteringMicrobiology.

Hepatitis Type	Pathogen	Symptoms	Incubation Period	Method of Transmission	Diagnostic Test	Treatment	Vaccine
A	Hepatitis A virus, Picornaviridae	Mostly subclinical; fever, headache; malaise, jaundice in severe cases; no chronic disease	2–6 weeks	Ingestion	IgM antibodies	Immunoglobulin	Inactivated virus. Post-exposure immune globulin
B	Hepatitis B virus, Hepadnaviridae	Frequently subclinical; similar to HAV, but no headache; more likely to progress to severe liver damage; chronic disease occurs	4–26 weeks	Parenteral; sexual contact	IgM antibodies	Interferon alfa and nucleoside analogues	Genetically modified vaccine produced in yeast
C	Hepatitis C virus, Flaviviridae	Similar to HBV, more likely to become chronic	2–22 weeks	Parenteral	PCR for viral RNA	Peginterferon and ribavirin	None
D	Hepatitis D virus, Deltaviridae	Severe liver damage; high mortality rate; chronic disease may occur	6–26 weeks	Parenteral; requires coinfection with hepatitis B	IgM antibodies	None	HBV vaccine is protective
E	Hepatitis E virus, Caliciviridae	Similar to HAV, but pregnant women may have high mortality; no chronic disease	2–6 weeks	Ingestion	IgM antibodies, PCR for viral RNA	None	HAV vaccine is protective

to her infant, usually at birth. In most cases, this type of transmission can be prevented by administering hepatitis B immune globulin (HBIG) to the newborn immediately after birth. These babies should also be vaccinated.

A third of the world's population shows serological evidence of past infection, but most people have cleared the virus. More than 350 million people have become chronic carriers of the virus. Most of these carriers are Asians and Africans, with a considerable proportion from Mediterranean countries. They acquired the infection at birth or in the first couple of years after birth. Many chronic carriers eventually die of liver cancer or cirrhosis (hardening and degeneration; see photo at the top of this page) of the liver.

Infection by HBV can take a varied path. There is a marked difference between acute and chronic HBV infection. If an individual is infected with HBV, acute hepatitis can result. Most such cases will resolve spontaneously as the patient clears the virus. About 5% of cases of acute hepatitis B will progress to chronic hepatitis B.

Acute Hepatitis B Many cases of acute hepatitis B are subclinical; the infected person is often entirely unaware. In about a third of the cases, the patient exhibits symptoms of disease—the person feels unwell and often suffers from low-grade fever, nausea, and abdominal pain. Eventually, jaundice, dark urine, and other evidence of liver damage appears. A long period of gradual recovery marked by fatigue and malaise follows as the damaged liver recovers. However, in a few cases (less than 1%), the patient develops *fulminant hepatitis,* causing sudden, massive liver damage; survival without a liver transplant is uncommon. If a case of hepatitis persists for more than 6 months, the condition is considered to have become chronic.

Chronic Hepatitis B Most individuals suffering from acute hepatitis B clear the virus successfully, but some fail to do so and develop chronic hepatitis B. People infected when very young are the most likely to become chronic carriers. The risk for infants is about 90%; in children of 1 to 5 years, about 25–50%. Adolescents and young adults have a much lower risk, only 6–10%. Overall, up to 10% of infected patients become chronic carriers of the virus. For some, the condition is essentially asymptomatic: they are considered inactive carriers and have a low risk of progressing to clinical disease. Many others suffer from malaise, loss of appetite, and general fatigue—but usually without evidence of jaundice. In cases in which the chronic infection results in liver cirrhosis, the patient becomes seriously ill. Tests of liver function usually follow, leading to a diagnosis. Without treatment, the prognosis is poor but this varies. Liver cancer develops in some cases. In fact, liver cancer is the most prevalent form of cancer in sub-Saharan Africa and East Asia, areas where hepatitis B is extremely common.

Hepatitis is a worldwide disease, but there is a significant difference in the clinical expression of hepatitis between areas of high prevalence and those of low prevalence.

In high-prevalence (Asian) countries, HBV infection tends to be acquired around the time of birth (perinatal) from infected mothers. As a consequence, the immune system doesn't recognize a difference between the virus and the host, and a high level of immunologic tolerance ensues. Because of this tolerance, the infection isn't accompanied by acute hepatitis; instead, a chronic, usually lifelong infection is established. This is the case in about 90% of infected persons. In spite of the immunologic tolerance to HBV, some liver injury occurs, and there is a high risk of death from liver disease, especially among men.

By contrast, in low-prevalence (Western) countries, most acute infections by HBV occur from exposure to infected blood or other body fluids. It is often a disease of young adults participating in risky behaviors—injection drug use or sexual promiscuity, for example. Long-term intimate nonsexual contact with an infected individual can also transmit HBV. Infected people who are immunocompetent develop a strong immune response, and the virus is cleared in all but about 1% of those infected. These patients have a much lower incidence of chronic disease and of liver cancer.

The diagnosis of HBV is usually based on symptoms, followed by tests of liver function. Serologic tests can detect HBV antigens and antibodies. The presence of hepatitis B surface antigen (HB_sAg) indicates the presence of the virus in the blood. After the virus is cleared, anti-HB_sA (surface antibody) appears, and the patient is considered immune. Detection of the hepatitis B "e" antigen (HBeAg), a marker for the core of the virus, usually means that the virus is replicating vigorously. If this antigen disappears and is replaced by antibodies against it, this usually means that liver disease associated with viral reproduction has diminished. It also means that the patient is less infectious to others.

Preventing HBV infection involves several strategies. Important among them are precautions such as disposable needles and syringes and the use of barrier-type contraception. Screening of transfused blood has also greatly reduced the risk. The introduction of HBV vaccines has become widespread worldwide and is now part of the childhood immunization schedule in the United States. The incidence of HBV infections has declined sharply in areas in which the vaccine is in use, and eventual elimination of the disease is conceivable.

It hasn't been possible to cultivate HBV in cell culture, a step that was necessary for the development of vaccines for polio, mumps, measles, and rubella. The available HBV vaccines use HB_sAg produced by a genetically modified yeast. Vaccination is recommended for high-risk groups; a partial listing would include health care workers exposed to blood and blood products, people undergoing hemodialysis, patients and staff at mental health care institutions, intravenous drug users (IDUs), and homosexually active men.

There is no specific treatment for acute HBV. For chronic HBV infection, there are currently seven approved treatments. However, none of these is reliably curative, largely because the DNA of the virus becomes integrated into the genome of the host. The aim of treatment for chronic HBV infections is to diminish the DNA of the virus to levels that are undetectable with a PCR assay.

Treatment decisions are made on the basis of several factors, such as patient age and the stage of the disease. Coinfections with HIV often occur and complicate treatment. Available antivirals include alpha interferon (the generic name is interferon alfa) and peginterferon (see page 460 for a discussion of interferons) as well as several nucleoside analogues, such as lamivudine,

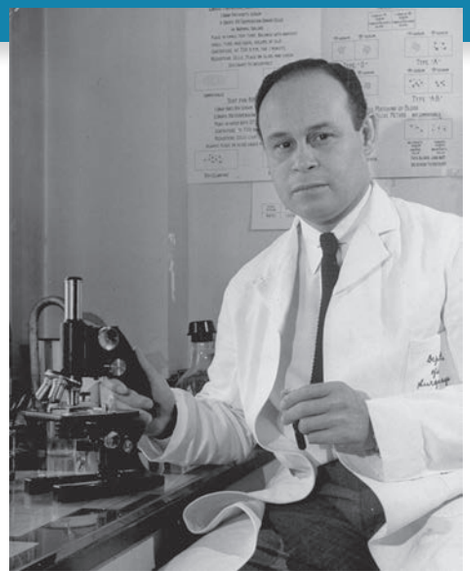
A Safe Blood Supply

Prior to blood banking, a physician typed the blood of a patient's friends until the proper blood type was found. In the 1940s, blood banking became the role of specialists. An important advance in protecting the blood supply from infectious agents was the 1979 change to an all-volunteer donor system. (Volunteer donors have a lower infection rate than paid donors.)

The large number of hemophilia patients who became infected with HIV in the early 1980s raised new questions regarding the safety of the blood supply. Serological tests are now routinely performed on donated blood to detect the presence of selected viruses, bacteria, and protozoa.

Unfortunately, serological tests may not detect contamination in the blood of newly infected donors because of the delay between the time of infection and the appearance of antibodies. Now, virtually all whole blood and plasma donations are screened for HCV, HIV, and West Nile virus by nucleic acid testing (NAT), which detects the virus nucleic acids directly. NAT has reduced the window of delay for detecting a newly acquired infection to approximately 25 days for HCV and 12 days for HIV. However, NAT takes several days to complete. Platelets, which become outdated in 5 days, are released before NAT has been completed.

Concern over potential contamination of blood by HIV led to the policy of disallowing blood from men who have sex with men. New technologies can clean blood by removing 99.9% of white blood cells, which harbor many viruses. Other new techniques inactivate any bacteria or viruses in the blood. The American Red Cross already requires virus-inactivating treatment of blood plasma.



American physician Charles Drew invented the technique for plasma separation that allowed blood to be stored, or "banked."

The goal is to make the blood supply as safe as possible. Synthetic blood substitutes may one day replace the need for donor blood.

adefovir, entecavir, telbivudine, and tenofovir DF. The course of treatment typically extends over several months. Combinations of at least two drugs are recommended to minimize development of resistance. Liver transplantation is often a final option in treatment.

Hepatitis C

In the 1960s, a previously unsuspected form of transfusion-transmitted hepatitis, now called **hepatitis C,** appeared. This new form of hepatitis soon constituted almost all transfusion-transmitted hepatitis—as testing eliminated HBV in the blood supply. Eventually, serological tests to detect hepatitis C virus (HCV) antibodies were developed that similarly reduced the transmission of HCV to very low levels. However, there is a delay of about 70 to 80 days between infection and the appearance of detectable HCV antibodies. The presence of HCV in contaminated blood cannot be detected during this interval, and about 1 in 100,000 transfusions can still result in infection. Blood-collecting facilities in the United States can now detect HCV-contaminated blood within 25 days of infection. (See the Applications of Microbiology box on safety of the blood supply). A PCR test can detect viral RNA within 1 to 2 weeks after infection.

HCV has a single strand of RNA and is enveloped. The virus doesn't kill the infected cell, but it triggers an immune inflammatory response that either clears the infection or slowly destroys the liver. (See the photo on page 728.) The virus is capable of rapid genetic variation to evade the immune system. This characteristic, along with the fact that currently it's cultured very inefficiently, complicates the search for an effective vaccine.

Hepatitis C has been described as a silent epidemic, killing more people than AIDS in the United States. It is often clinically inapparent—few people have recognizable symptoms until about 20 years have elapsed. Probably as many as a third of individuals infected with HCV clear the virus spontaneously. Even today, probably only a minority of infections have been diagnosed. Often, hepatitis C is detected only during some routine testing, such as for insurance or blood donation. A majority of cases, perhaps as high as 85%, progress to chronic hepatitis, a much higher rate than with HBV. Surveys indicated an estimated 3.2 million of the U.S. population are chronically infected. About 25% of chronically infected patients develop liver cirrhosis or liver cancer. Hepatitis C is probably the major reason for liver transplantation. Persons infected with HCV should be immunized against both HAV and HBV (a combination vaccine is now available) because they cannot afford the risk of further liver damage.

Preventing HCV is limited to minimizing exposure—even sharing of items such as razors, toothbrushes, or nail clippers is dangerous. A common source of infection is the sharing of injection equipment among IDUs. At least 80% of this group is infected with HCV. In one exceptional case, the disease was transmitted by means of a straw shared for inhaling cocaine. Interestingly, in more than one-third of the cases, a mode of transmission—by

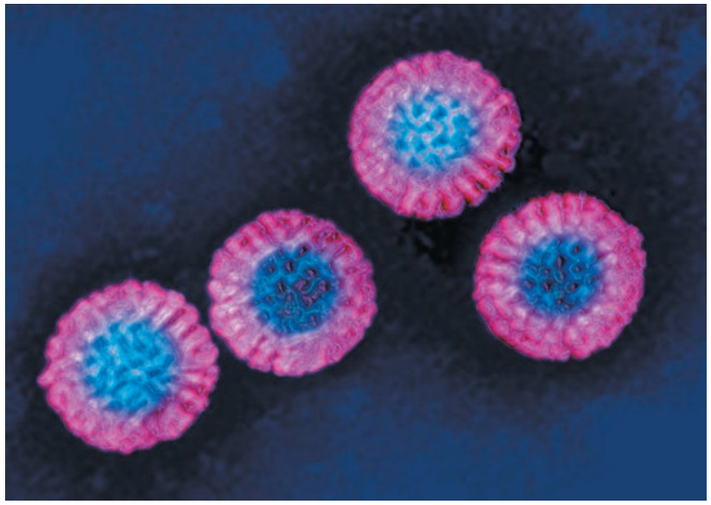


Figure 25.15 ***Rotavirus.*** This negatively stained electron micrograph shows the morphology of the *rotavirus* (*rota* = wheel), which gives the virus its name.

Q What disease does *rotavirus* cause?

contaminated blood, sexual contact, or other means—cannot be identified.

The treatment of choice is a drug combination, peginterferon and ribavirin. Its disadvantages are that it is very expensive and requires a regimen of months. It also has many potentially severe side effects. However, complete eradication of HCV is attained in many cases. A combination of three drugs, a protease inhibitor, a nucleoside analog, and a non-nucleoside polymerase inhibitor, are approved as promising treatments for patients who haven't responded to other drugs.

Other Hepatitis Viruses

Hepatitis D can occur as either acute (*coinfection form*) or chronic (*superinfection form*) hepatitis. In people with a case of self-limiting acute hepatitis B, coinfection with HDV disappears as the HBV is cleared from the system, and the condition resembles a typical case of acute hepatitis B. However, if the HBV infection progressed to the chronic stage, superinfection with HDV is often accompanied by progressive liver damage and a fatality rate several times that of people infected with HBV alone.

Hepatitis D is linked to the epidemiology of hepatitis B. In the United States and northern Europe, the disease occurs predominantly in high-risk groups, such as IDUs.

Hepatitis E (HEV) is spread by fecal–oral transmission, much like hepatitis A, which it clinically and structurally resembles. It is endemic in areas with poor sanitation, especially India and Southeast Asia. HEV does not cause chronic liver disease, but for some unexplained reason it is responsible for a mortality rate in excess of 20% in pregnant women.

CHECK YOUR UNDERSTANDING

Of the several hepatitis diseases, HAV, HBV, HCV, HDV, and HEV, which two now have effective vaccines to prevent them? **25-6**

Viral Gastroenteritis

Acute gastroenteritis is one of the most common diseases of humans. About 90% of cases of acute viral gastroenteritis are caused by either the *Rotavirus* or the human caliciviruses, better known as the Norwalk family of viruses now in the *Norovirus*.

Rotavirus

Rotavirus (Figure 25.15) is probably the most common cause of viral gastroenteritis, especially in children. It's estimated to cause about 3 million cases, but fewer than 100 deaths, every year in the United States. Mortality is much higher in less developed countries because rehydration therapy isn't as available. More than 90% of children in the United States have been infected by the age of 3. In some cases, parents also become infected. Acquired immunity then makes *rotavirus* infections,

Clinical Case

The health department makes a visit to the petting zoo to investigate the animals with which Anna had contact. Rectal swabs or fecal samples are cultured from the various animals at the zoo (see the table.)

Isolation of STEC O157 from Fecal Sample/Rectal Swabs Collected at the Petting Zoo

Animal(s)	No. of Animals	No. of Animals with Isolates Identical to the DNA Pattern of Anna's STEC O157
Deer	8	1
Donkey	1	0
Goats	8	2
Guinea fowl	5	0
Llama	1	0
Peacock	1	0
Pig	1	0
Rabbits	10	0
Sheep	4	3

Based on these results, what is the most likely mode of transmission, and how can transmission be prevented?

except for certain strains, much less common in adults. In most cases, following an incubation period of 2 to 3 days, the patient suffers from low-grade fever, diarrhea, and vomiting, which persists for about a week.

Rotavirus cases usually peak during the cooler winter months. An infectious dose is estimated to be fewer than 100 viruses, and patients shed billions in every gram of stool. The first vaccine to prevent *rotavirus,* introduced in 1998, was withdrawn after serious problems developed. In 2006 a live, orally administered vaccine was licensed. *Rotavirus* infections are routinely diagnosed by several types of commercially available tests, such as enzyme immunoassays. Treatment is usually limited to oral rehydration therapy.

Norovirus

Noroviruses were first identified following an outbreak of gastroenteritis in Norwalk, Ohio, in 1968. The responsible agent was identified in 1972 and called the *Norwalk virus.* Several similar viruses were later identified, and this group was termed *Norwalk-like viruses.* All were determined to be members of the caliciviruses (named for the Latin *calyx,* meaning cup—cup-shaped depressions are visible on the viruses) and are now termed *noroviruses.* It is not practical to culture them, and they do not infect the usual laboratory animals. Humans become infected by fecal–oral transmission from food and water and even aerosols from vomiting. The infective dose may be as low as 10 viruses. The viruses continue to be shed for several days after the patient is asymptomatic. More than 20 million cases of *norovirus* gastroenteritis occur annually in the United States but only about 300 deaths. About half of adult Americans show serological evidence that they have been infected. (See the Clinical Focus box in Chapter 9, page 259.) The currently dominant strain of noroviruses made its appearance around 2002, which is attributed to several possible factors. This strain may be more virulent, or more environmentally stable; also, fewer people may have had resistance to it from previous exposure. Natural resistance to a particular strain may last only a few months—at most about 3 years.

Cleanup and prevention of transmission following an outbreak on a cruise ship or restaurant, for example, has proved to be a challenging problem. The viruses are unusually persistent on environmental surfaces including door handles or elevator buttons. The CDC recommends the use of sanitizing hand gels such as Purell, which contain >62% ethanol. The noroviruses don't have a lipid envelope and are, therefore, not reliably inactivated by ethanol. Most of the effectiveness of such measures is probably related to mechanical removal, as with hand soap. To decontaminate hard, nonporous surfaces requires solutions containing 1000 to 5000 ppm of hypochlorite (a 1:50 or 1:10 solution of 5.26% bleach, respectively). The EPA recommends use of a peroxygen compound (see page 194) called Virkon-S for surface decontamination.

To detect noroviruses in stool samples, laboratories use sensitive PCR and EIA tests. The availability of such new and sensitive assays has led to recognition of noroviruses as the most common cause (at least half of recent foodborne outbreaks in the United States) of nonbacterial gastroenteritis.

Following an incubation period of 18 to 48 hours, the patient suffers from vomiting and/or diarrhea for 2 or 3 days. Diarrhea is the most prevalent symptom in children; most adults experience diarrhea, although many adult patients experience only vomiting. The severity of symptoms often depends upon the size of the infective dose.

The only treatment for viral gastroenteritis is oral rehydration or, in exceptional cases, intravenous rehydration.

Viral diseases of the GI tract are summarized in Diseases in Focus 25.4.

CHECK YOUR UNDERSTANDING

Two very common causes of viral gastroenteritis are caused by rotaviruses and noroviruses. Which of these now can be prevented by a vaccine? **25-7**

Fungal Diseases of the Digestive System

LEARNING OBJECTIVE

25-8 Identify the causes of ergot poisoning and aflatoxin poisoning.

Some fungi produce toxins called *mycotoxins* that cause blood diseases, nervous system disorders, kidney damage, liver damage, and even cancer. Mycotoxin intoxication is considered when multiple patients have similar clinical signs and symptoms. Diagnosis is usually based on finding the fungi or mycotoxins in food (Diseases in Focus 25.5, page 737).

Ergot and Aflatoxin Poisoning

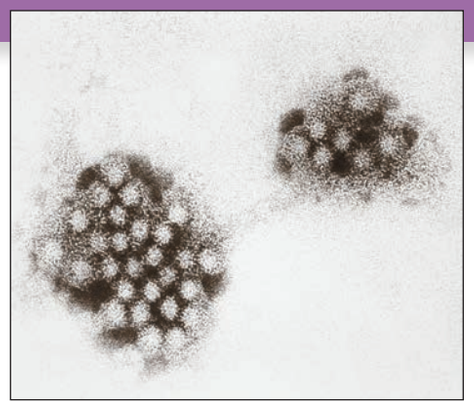
Mycotoxins produced by *Claviceps purpurea* (KLA-vi-seps pur-pur-Ē-ah), a fungus causing smut infections on grain crops, cause **ergot poisoning** when rye or other cereal grains contaminated with the fungus are ingested. The toxin can restrict blood flow in the limbs, with resulting gangrene. It may also cause hallucinogenic symptoms, producing bizarre behavior similar to that caused by LSD.

Aflatoxin is a mycotoxin produced by the fungus *Aspergillus flavus,* a common mold. It has been found in many foods but is particularly likely to be found on peanuts. **Aflatoxin poisoning** can cause serious damage to livestock when their feed is contaminated with *A. flavus.* Although risk to humans is unknown, there is strong evidence aflatoxin contributes to cirrhosis of the liver and cancer of the liver in parts of the world, such as India and Africa, where food is subject to aflatoxin contamination.

DISEASES IN FOCUS 25.4

Viral Diseases of the Digestive System

An outbreak of diarrhea begins in mid-June, peaks in mid-August, and tapers off in September. A clinical case is defined as diarrhea (three loose stools during a 24-hour period) in a member of a swim club. The virus shown at right is isolated from one patient. Use the table below to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Virus cultured from the patient's stool.

Disease	Pathogen	Symptoms	Incubation Period	Diagnostic Test	Treatment
Mumps	Mumps virus, Paramyxoviridae	Painful swelling of parotid glands	16–18 days	Symptoms; virus culture	Preventive vaccine
Viral Gastroenteritis	*Rotavirus*	Vomiting, diarrhea for 1 week	1–3 days	Enzyme immuno-assay for viral antigens in feces	Oral rehydration
	Norovirus	Vomiting, diarrhea for 2–3 days	18–48 hr	PCR	Oral rehydration
Hepatitis (See Diseases in Focus 25.3 on page 728)					

CHECK YOUR UNDERSTANDING

What is the connection between the occasional hallucinogenic symptoms produced by ergot poisoning and a modern illicit drug? **25-8**

Protozoan Diseases of the Digestive System

LEARNING OBJECTIVE

25-9 List the causative agents, modes of transmission, symptoms, and treatments for giardiasis, cryptosporidiosis, *Cyclospora* diarrheal infection, and amebic dysentery.

Several pathogenic protozoa complete their life cycles in the human digestive system (Diseases in Focus 25.5, page 737). Usually they are ingested as resistant, infective cysts and are shed in greatly increased numbers as newly produced cysts.

Giardiasis

Giardia intestinalis (also known as *G. lamblia* and occasionally as *G. duodenalis*) is a flagellated protozoan that is able to attach firmly to a human's intestinal wall (**Figure 25.16**). In 1681, van Leeuwenhoek described them as having "bodies . . . somewhat longer than broad and their belly, which was flatlike, furnished with sundry little paws."

G. intestinalis is the cause of **giardiasis,** a prolonged diarrheal disease. Sometimes persisting for weeks, giardiasis is characterized by malaise, nausea, flatulence (intestinal gas), weakness, weight loss, and abdominal cramps. The distinctive odor of

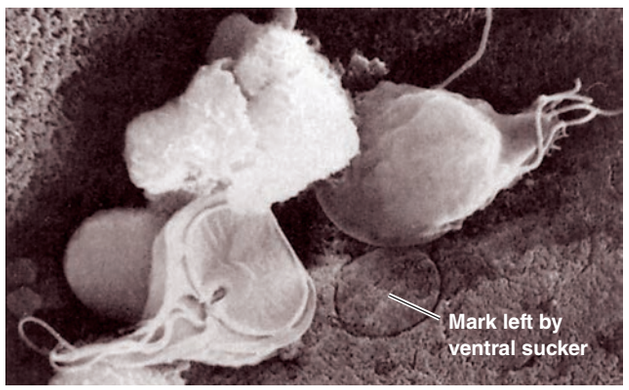


Figure 25.16 The trophozoite form of *Giardia intestinalis,* the flagellated protozoan that causes giardiasis. Notice the circular mark left on the intestinal wall by the ventral sucker disk the parasite uses to attach itself. The dorsal side is smoothly streamlined, and the intestinal contents move easily around the attached microorganism.

Q What is the string test for giardiasis?

hydrogen sulfide can often be detected in the breath or stools. The protozoa sometimes occupy so much of the intestinal wall that they interfere with food absorption.

Outbreaks of giardiasis in the United States occur often, especially during camping and swimming seasons. About 7% of the population are healthy carriers and shed the cysts in their feces. The pathogen is also shed by a number of wild mammals, especially beavers, and the disease occurs in backpackers who drink from untreated wilderness waters.

Most outbreaks are transmitted by contaminated water supplies. In a recent national survey of surface waters serving as sources for U.S. municipalities, the protozoan was detected in 18% of the samples. Because the cyst stage is relatively insensitive to chlorine, filtration or boiling of water supplies is usually necessary to eliminate the cysts from water.

Because *G. intestinalis* isn't reliably found in stool by microscopic examination, the *string test* is sometimes used for diagnosis. In this test, a gelatin capsule packed with about 140 cm of fine string is swallowed by the patient. One end of the string is taped to the cheek. The gelatin capsule dissolves in the stomach, and an enclosed weighted rubber bag attached to the other end of the string enters the upper bowel. After a few hours, the string is drawn up through the mouth and examined for trophozoite forms of *G. intestinalis.* Several commercially available ELISA tests detect both ova and the parasite in stool specimens. The CDC currently recommends a direct fluorescent-antibody (FA) test (see Figure 18.11a, page 508) for detecting cysts. These tests are especially useful for epidemiological screening. Testing of drinking water for *Giardia* is difficult but often necessary to prevent or trace disease outbreaks. These tests are frequently combined with tests for *Cryptosporidium* protozoa, discussed in the next section.

Treatment with metronidazole or quinacrine hydrochloride is usually effective within a week. The U.S. Food and Drug Administration (FDA) has recently approved a new oral drug, nitazoxanide, for both cryptosporidiosis (see Figure 25.17) and giardiasis. Like metronidazole, it affects anaerobic metabolic pathways, but it requires a shorter treatment regimen.

CHECK YOUR UNDERSTANDING

Is giardiasis caused by ingestion of a cyst or an oocyst? **25-9**

Cryptosporidiosis

Cryptosporidiosis is caused by the protozoan *Cryptosporidium.* The most prevalent species affecting humans are *C. parvum* and *C. hominis.* The term *cryptosporidiosis* (medical personnel often refer to it more simply as *crypto*) describes infections by either organism. Infection occurs when humans ingest the cryptosporidian oocysts (**Figure 25.17**). The oocysts eventually release sporozoites into the small intestine. The motile sporozoites invade the epithelial cells of the intestine and undergo a cycle that eventually releases oocysts to be excreted in the feces.

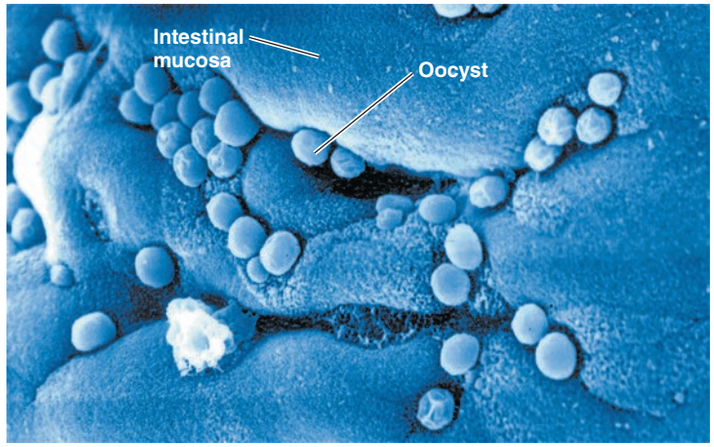


Figure 25.17 Cryptosporidiosis. Oocysts of *Cryptosporidium hominis* are shown here embedded in the intestinal mucosa.

How is cryptosporidiosis transmitted?

(Compare with the similar life cycle of *Toxoplasma gondii* in Figure 23.23, page 663). The disease is a cholera-like diarrhea of 10 to 14 days duration. In immunodeficient individuals, including AIDS patients, the diarrhea becomes progressively worse and is life-threatening.

The infection is transmitted to humans largely through recreational and drinking water systems contaminated with oocysts of *Cryptosporidium,* mostly from animal wastes, especially cattle. Studies in the United States show that many, if not most, lakes, streams, and even wells are contaminated. The oocysts, like the cysts of *G. intestinalis,* are resistant to chlorination and must be removed from water by filtration. Even filtration sometimes fails. This is especially true of swimming pools, where both chlorination and filtration systems are ineffective in removing oocysts. Alternatives to routine chlorination are ultraviolet radiation, ozonation, and chlorine dioxide. See the Clinical Focus box in Chapter 12, page 347. An infective dose may be as low as ten oocysts. Fecal–oral transmission resulting from poor sanitation also occurs; many outbreaks have occurred in day-care settings.

Testing of water is important, but the currently available methods have been described as being cumbersome, time-consuming, and inefficient. Most widely used is an FA test that can simultaneously detect both *G. intestinalis* cysts and *Cryptosporidium* oocysts. Regular water testing will probably become mandatory, and research for simpler and more reliable methods has a high priority in public health science.

The recommended drug for treatment is the newly introduced nitazoxanide, which is also effective in treating giardiasis.

Cryptosporidiosis is most reliably diagnosed in the laboratory by detecting oocysts in fecal samples by microscopic examination, sometimes accompanied by assays for antibodies

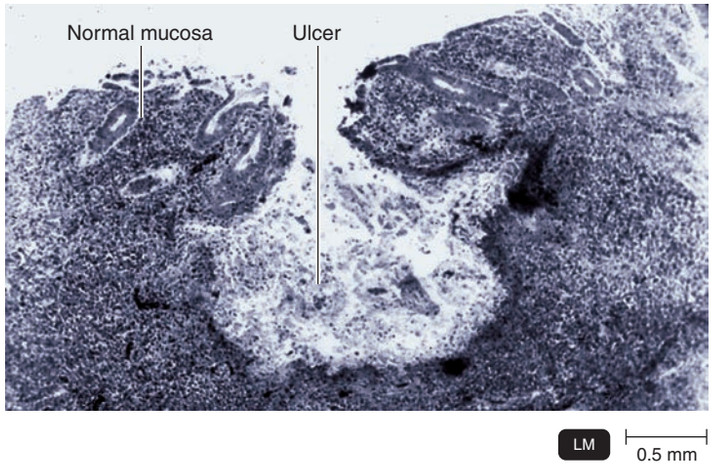


Figure 25.18 Section of intestinal wall showing a typical flask-shaped ulcer caused by *Entamoeba histolytica*.

If this lesion progressed far enough, could it be life-threatening?

by FA tests. The direct FA test is considered the "gold standard." The presence of oocysts or sporozoite antigens in fecal samples can also be determined by the use of immunoassay tests that are commercially available.

Cyclospora Diarrheal Infection

A protozoan discovered in 1993 is responsible for a series of recent diarrheal disease outbreaks. The pathogen has since been named *Cyclospora cayetanensis*.

The symptoms of ***Cyclospora* diarrheal infection** are a few days of watery diarrhea, but in some cases it may persist for weeks. The disease is especially debilitating for immunosuppressed people, such as AIDS patients. It is uncertain whether humans are the only host for the protozoan. Most outbreaks have been associated with the ingestion of oocysts in water, on contaminated berries, or similar uncooked foods. The foods are presumed to have been contaminated by oocysts shed in human feces or possibly from birds in the field.

Microscopic examination can identify the oocysts, which are about twice the diameter of those of *Cryptosporidium*. There is really no satisfactory test to detect contamination of foods. The antibiotic combination of trimethoprim and sulfamethoxazole is used for treatment.

Amebic Dysentery (Amebiasis)

Amebic dysentery, or **amebiasis,** is spread mostly by food or water contaminated by cysts of the protozoan ameba *Entamoeba histolytica* (see Figure 12.19b, page 340). Although stomach acid can destroy trophozoites, it does not affect the cysts. In the intestinal tract, the cyst wall is digested away, and the trophozoites are released. They then multiply in the epithelial cells of the wall of the large intestine. A severe dysentery results; the feces characteristically contain blood and mucus. The trophozoites feed on tissue in the gastrointestinal tract (Figure 25.18).

Severe bacterial infections result if the intestinal wall is perforated. Abscesses might have to be treated surgically, and the invasion of other organs, particularly the liver, is not uncommon. Perhaps 5% of the U.S. population are asymptomatic carriers of *E. histolytica*. Worldwide, one person in ten is estimated to be infected, mostly asymptomatically, and about 10% of these infections progress to the more serious stages.

Diagnosis largely depends on recovering and identifying the pathogens in feces. (Red blood cells, ingested as the parasite feeds on intestinal tissue and observed within the trophozoite stage of an ameba, help identify *E. histolytica*.) Several serological tests can also be used for diagnosis, including latex agglutination and fluorescent-antibody tests. Such tests are especially useful when the affected areas are outside the intestinal tract and the patient is not passing amebae.

Metronidazole plus iodoquinol are the drugs of choice in treatment.

Helminthic Diseases of the Digestive System

LEARNING OBJECTIVE

25-10 List the causative agents, modes of transmission, symptoms, and treatments for tapeworms, hydatid disease, pinworms, hookworms, whipworms, ascariasis, and trichinellosis.

Helminthic parasites are very common in the human intestinal tract, especially in warm, moist regions where sanitation is poor. Figure 25.19 shows the worldwide estimated incidence of infection with some intestinal helminths. These diseases are called *neglected tropical diseases (NTD)* (see the Big Picture pages 622–623) because

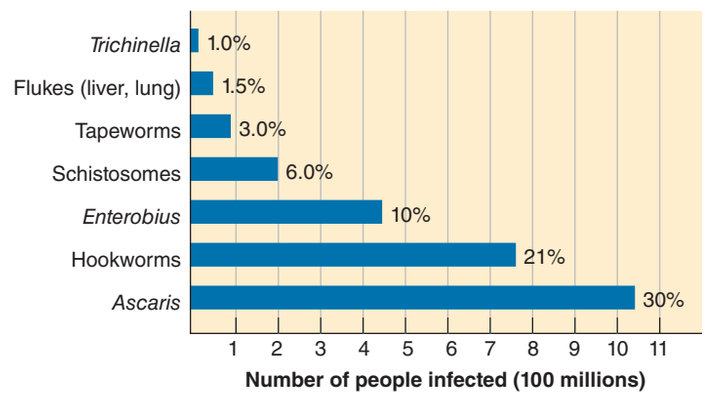


Figure 25.19 The worldwide prevalence of human infections with selected intestinal helminths. Two billion people are infected.
Source: World Health Organization.

How is each of these diseases transmitted?

they kill 500,000 people annually in the poorest countries and are not yet controlled. In spite of the parasites' size and formidable appearance, light infections often produce few symptoms. They have become so well adapted to their human hosts, and vice versa, that when their presence is revealed, it is often a surprise. Heavy infections can cause a range of symptoms described below.

Tapeworms

The life cycle of a typical **tapeworm** extends through three stages. The adult worm lives in the intestine of a human host, where it produces eggs that are excreted in the feces (see Figure 12.27, page 348). The eggs are ingested by animals such as grazing cattle, where the egg hatches into a larval form called a *cysticercus* (plural: *cysticerci*) that lodges in the animal's muscles. Human infections by tapeworms begin with the consumption of undercooked beef, pork, or fish containing cysticerci. The cysticerci develop into adult tapeworms that attach to the intestinal wall by suckers on the scolex (see the photo in Figure 12.27).

The adult beef tapeworm, *Taenia saginata* (TE-nē-ah sa-jin-AH-tah), seldom causes significant symptoms beyond a vague abdominal discomfort. However, psychological distress can result when a meter or more of detached segments (proglottids) occasionally break loose and unexpectedly slip out of the anus.

Taenia solium (SŌ-lē-um), the pork tapeworm, has a life cycle similar to that of the beef tapeworm. An important difference is that *T. solium* may produce the larval stage in the human host. **Taeniasis** develops when the adult tapeworm infects the human intestine. This is a generally benign, asymptomatic condition, but the host continuously expels eggs of *T. solium,* which contaminate hands and food under poor sanitary conditions. **Cysticercosis,** infection with the larval stage, can develop when humans or swine ingest *T. solium* eggs. These eggs can leave the digestive tract and develop into larvae that lodge in tissue (usually brain or muscles). Cysticerci in muscle tissue are relatively benign and cause few serious symptoms, but the larvae occasionally lodge in an eye, causing **ophthalmic cysticercosis** and affecting vision (**Figure 25.20**). The most serious, and much more common, disease is **neurocysticercosis,** which arises when the larvae develop in areas of the central nervous system, such as the brain. Neurocysticercosis, which is endemic in Mexico and Central America, has become a fairly common condition in parts of the United States with large Mexican and Central American immigrant populations.

The symptoms often mimic those of epilepsy or a brain tumor. The number of cases reported reflects, in part, the use of computed tomography (CT) scanning or magnetic resonance imaging (MRI) in diagnosis. In endemic areas, neurological patients can be screened with serological tests for antibodies to *T. solium.*

The fish tapeworm *Diphyllobothrium latum* (dī′fil-lō-BAH-thrē-um LĀ-tum) is found in pike, trout, perch, and salmon. The CDC has issued warnings about the risks of fish tapeworm infection from sashimi and sushi (Japanese dishes prepared from raw fish), foods that have become increasingly popular. To relate a vivid example, about 10 days after eating, one person developed symptoms of abdominal distention, flatulence, belching, intermittent abdominal cramping, and diarrhea. Eight days later, the patient passed a tapeworm 1.2 m (4 ft) long, identified as a species of *Diphyllobothrium.*

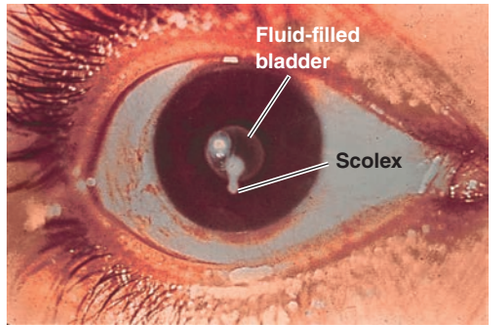


Figure 25.20 Ophthalmic cysticercosis. Some cases of cysticercosis affect the eye.

Q What organ is most likely to be affected by neurocysticercosis?

Laboratory diagnosis of tapeworms consists of identifying the tapeworm eggs or segments in feces. Adult tapeworms in the intestinal stage can be eliminated with antiparasitic drugs such as praziquantel and albendazole. Cases of neurocysticercosis can sometimes be treated with drugs, but these often worsen the situation, and surgery may be required to remove cysticerci.

CHECK YOUR UNDERSTANDING

✓ What species of tapeworm is the cause of cysticercosis? **25-10**

Hydatid Disease

One of the most dangerous tapeworms is *Echinococcus granulosus* (ē-KĪ-nō-kok′kus gran-ū-LŌ-sus), which is only a few millimeters in length (see Figure 12.28, page 349). The disease occurs most frequently in people who raise sheep or hunt or trap wild animals.

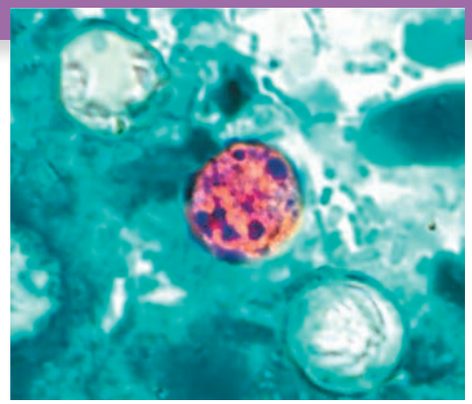
Once ingested by a human, the eggs of *E. granulosus* may migrate to various tissues of the body. The liver and lungs are the most common sites, but the brain and numerous other sites also may be infected. Once in place, the egg develops into a **hydatid cyst** that can grow to a diameter of 1 cm in a few months (**Figure 25.21**). In some locations, cysts may not be apparent for many years. Some, where they are free to expand, become enormous, containing up to 15 liters (4 gallons) of fluid.

Damage may arise from the size of the cyst in such areas as the brain or the interior of bones. If the cyst ruptures in the host, it can lead to the development of a great many daughter cysts. Another factor in the pathogenicity of such cysts is that the fluid contains proteinaceous material to which the host becomes sensitized. If the cyst suddenly ruptures, the result can be life-threatening anaphylactic shock.

DISEASES IN FOCUS 25.5

Fungal, Protozoan, and Helminthic Diseases of the Lower Digestive System

Public health officials in Pennsylvania are notified of cases of watery diarrhea, with frequent, sometimes explosive, bowel movements among persons associated with a residential facility (e.g., residents, staff, and volunteers). The disease is associated with eating snow peas. Use the table below to identify possible causes of these symptoms. For the solution, go to MasteringMicrobiology.



Acid-fast stain from the patient's feces.

Disease	Pathogen	Symptoms	Reservoir or Host	Diagnostic Test	Treatment
FUNGAL DISEASES					
Ergot Poisoning	*Claviceps purpurea*	Restricted blood flow to limbs; hallucinogenic.	Mycotoxin produced by fungus growing on grains	Finding fungal sclerotia in food	None
Aflatoxin Poisoning	*Aspergillus flavus*	Liver cirrhosis; liver cancer.	Mycotoxin produced by fungus growing on food	Immunoassay for toxin in food	None
PROTOZOAN DISEASES					
Giardiasis	*Giardia intestinalis*	Protozoan adheres to intestinal wall, may inhibit nutritional absorption; diarrhea.	Water; mammals	FA	Metronidazole; quinacrine
Cryptosporidiosis	*Cryptosporidium hominis, C. parvum*	Self-limiting diarrhea; may be life-threatening in immunosuppressed patients.	Cattle; water	Acid-fast stain; FA; ELISA	Oral rehydration
***Cyclospora* Diarrheal Infection**	*Cyclospora cayetanensis*	Watery diarrhea.	Humans; birds; usually ingested with fruits and vegetables	Acid-fast stain	Trimethoprim and sulfamethoxazole
Amebic Dysentery (amebiasis)	*Entamoeba histolytica*	Ameba lyses epithelial cells of intestine, causes abscesses; significant mortality rate.	Humans	Microscopy; serology	Metronidazole
HELMINTHIC DISEASES					
Tapeworms	*Taenia saginata, T. solium, Diphyllobothrium latum*	Helminth leaves few symptoms; pork tapeworm larvae may encyst in many organs (neurocysticercosis) and cause damage.	Intermediate host: cattle, pigs, fish; definitive host: humans	Microscopic exam of feces	Praziquantel; albendazole
Hydatid Disease	*Echinococcus granulosus*	Larvae form in body; may be very large and cause damage.	Intermediate host: humans; definitive host: dogs	Serology; X-ray exam	Surgical removal; albendazole
Pinworms	*Enterobius vermicularis*	Itching around anus.	Intermediate and definitive hosts: humans	Microscopic exam	Pyrantel pamoate
Hookworms	*Necator americanus, Ancyclostoma duodenale*	Large infections may result in anemia.	Larvae enter skin from soil; definitive hosts: humans	Microscopic exam	Mebendazole
Ascariasis	*Ascaris lumbricoides*	Helminths live off undigested intestinal contents, causing few symptoms.	Intermediate and definitive hosts: humans	Microscopic exam	Mebendazole
Whipworm	*Trichuris trichiura*	Diarrhea, malnutrition.	Intermediate and definitive hosts: humans	Microscopic exam of feces	Albendazole, mebendazole
Trichinellosis	*Trichinella spiralis, T. nativa*	Larvae encyst in striated muscle; usually few symptoms, but large infections may be fatal.	Intermediate and definitive hosts: mammals (including humans)	Biopsy; ELISA	Mebendazole; corticosteroids

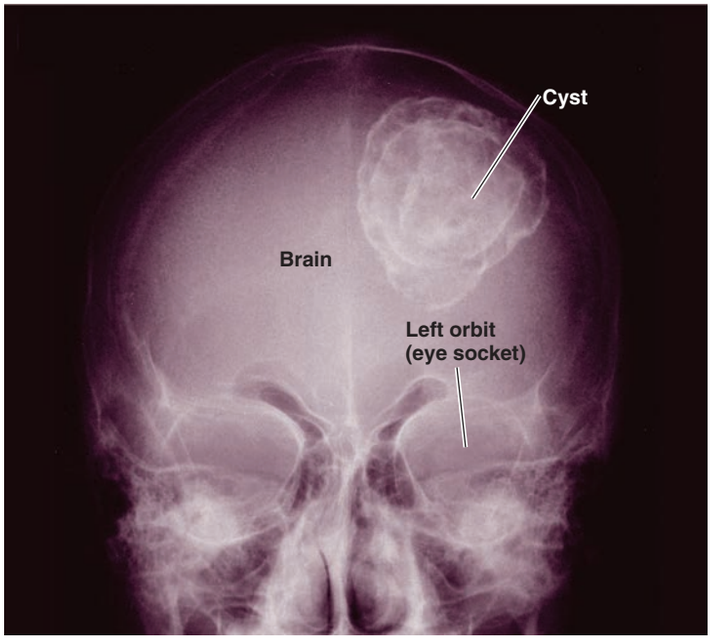


Figure 25.21 A hydatid cyst formed by *Echinococcus granulosus.* A large cyst can be seen in this X-ray image of the brain of an infected individual.

How do hydatid cysts affect the body?

For diagnosis, several serological tests that detect circulating antibodies are useful in screening. If available, physical imaging methods such as X rays, CT, and MRI are best.

Treatment is usually surgical removal, but care must be taken to avoid release of the fluid and the potential spread of infection or anaphylactic shock. If removal isn't feasible, the drug albendazole can kill the cysts.

Nematodes

Pinworms

Most of us are familiar with the **pinworm,** *Enterobius vermicularis* (see Figure 12.29, page 350). This tiny worm (females are 8–13 mm in length, males 2–5 mm) migrates out of the anus of the human host to lay its eggs, causing local itching. Whole households may become infected. Diagnosis is usually based on finding eggs around the anus. These can be viewed by pressing transparent cellulose tape, sticky side down, against the skin, transferring the tape to a microscope slide and viewing the slide under a microscope. Such drugs as pyrantel pamoate (often available without a prescription) and mebendazole are usually effective in treatment.

Hookworms

Hookworm infections were once a very common parasitic disease in the southeastern states. In the United States, the species most often seen is *Necator americanus.* Another species, *Ancylostoma duodenale,* is widely distributed around the world.

The hookworm attaches to the intestinal wall and feeds on blood and tissue rather than on partially digested food (Figure 25.22), so the presence of large numbers of worms can lead to anemia and lethargic behavior. Heavy infections can also lead to a bizarre symptom known as *pica,* a craving for peculiar foods, such as laundry starch or soil containing a certain type of clay. Pica is a symptom of iron deficiency anemia.

Because the life cycle of the hookworm requires human feces to enter the soil and bare skin to contact contaminated soil, the incidence of the disease has declined greatly with improved sanitation and the practice of wearing shoes. Hookworm infections are diagnosed by finding parasite eggs in feces and can be treated effectively with mebendazole.

Ascariasis

One of the most widespread helminthic infections is **ascariasis,** caused by *Ascaris lumbricoides.* This condition is familiar to many American physicians. In the southeastern United States it is quite common, with a reported incidence of 20–60% in the childhood population. Worldwide, perhaps 30% of the population is infected. Diagnosis is often made when an adult worm emerges from the anus, mouth, or nose (see Chapter 12, page 349). These worms can be quite large, up to 30 cm (about 1 ft) in length (Figure 25.23). In the intestinal tract, they live on partially digested food and cause few symptoms.

The worm's life cycle begins when eggs (upwards of 200,000 per day) are shed in a person's feces and, under poor sanitary conditions, are ingested by another person. In the upper intestine, the eggs hatch into small wormlike larvae that pass into the bloodstream and then into the lungs. There they migrate into the throat and are swallowed. The larvae develop into egg-laying adults in the intestines.

In the lungs, the tiny larvae may cause some pulmonary symptoms. Extremely large numbers may block the intestine,

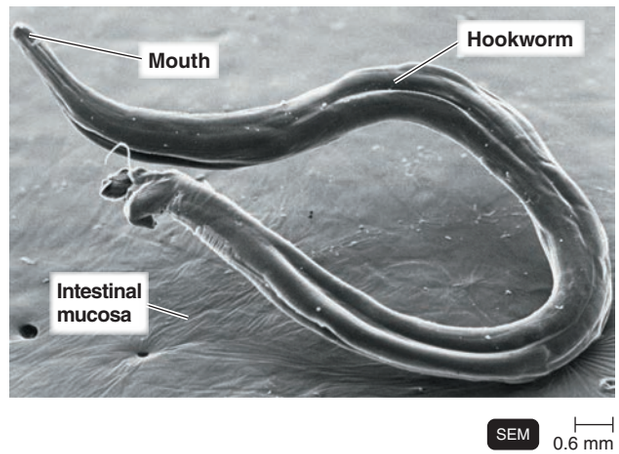


Figure 25.22 *Ancylostoma* hookworm. The mouth of the hookworm is adapted to attachment and feeding on tissue. Males are typically 8–11 mm in length, females 10–13 mm.

Why can a hookworm infection lead to anemia?



Figure 25.23 ***Ascaris lumbricoides,* the cause of ascariasis.** These intestinal worms are large, the female up to about 30 cm in length.

Q What are the principal features of the life cycle of *A. lumbricoides*?

bile duct, or pancreatic duct. The worms do not usually cause severe symptoms, but their presence can be manifested in distressing ways. The most dramatic consequences of infection with *A. lumbricoides* are from the migrations of adult worms. Worms have been known to leave the body of small children through the umbilicus (navel) and to escape through the nostrils of a sleeping person. Microscopic examination of feces for eggs is used for diagnosis. Once ascariasis is diagnosed, it can be effectively treated with mebendazole or albendazole.

Whipworm (*Trichuris trichiura*)

Whipworm infestations, known as *trichuriasis,* are widespread in tropical areas of the world, especially Asia. The nematode's name, *Trichuris trichiura* (Greek *trichos* = a hair, and *oura* = tail), is derived from its morphology. The worms are 30 to 50 mm in length. The main body is thin and hairlike, but the posterior end abruptly becomes thick, resembling a coiled whip with a handle—therefore, the common name of *whipworm.* In the United States, its distribution and incidence are similar to those of *A. lumbricoides.* Medical technicians microscopically inspecting fecal samples will occasionally encounter the whipworm's distinctive egg (**Figure 25.24**). Nationally, eggs are present in a little over 1% of the population. In southeastern states, children pick up infective eggs from contaminated soil; in that area of the United States, the incidence of whipworm in children is about 20%.



Figure 25.24 **Egg of *Trichuris trichiura.*** This distinctive egg resembles a tea tray with handles.

Q How is trichuriasis transmitted?

When an embryonated egg is ingested, it hatches and enters the intestinal glands (crypts of Lieberkühn, deep crevices lined with cells that secrete intestinal juice). There the worm grows and slowly begins to tunnel back to the interior intestinal surface. Eventually, the worm positions itself such that the posterior end extends into the intestinal lumen and the hairlike anterior remains buried in the mucosa. The worm lives there for several years as a tissue parasite, feeding on cell contents and blood. Light infections of fewer than 100 worms usually pass unnoticed, but very heavy infestations may cause abdominal pain and diarrhea. Trichuriasis can also lead to anemia and malnutrition, resulting in significant weight loss and retarded growth. Treatment is with mebendazole or albendazole, although most cases do not require medical attention.

Clinical Case Resolved

Because Anna was in contact with three different animals that have an identical strain of *E. coli,* it is more than likely she became infected from the animals at the petting zoo. Petting-zoo–associated STEC O157 has been linked to direct animal contact (i.e., touching or feeding), indirect contact (e.g., touching sawdust or shavings), and exposure from contaminated clothes, shoes, strollers, or other fomites.

Petting zoo visits are popular leisure activities and also have become an important feature of education for children. Visitors of petting zoos appear to face only a small risk of becoming infected with STEC O157 from the livestock or the farm environment, given the relatively small number of human cases each year in proportion to the large number of visitors. Cattle and other ruminants, such as sheep and goats, are important natural reservoirs of STEC O157. It isn't practical to try to exclude animals carrying STEC O157, because they usually don't show clinical symptoms, and shedding appears to be intermittent and transient. Colonization of cattle with STEC O157 typically lasts 2 months or less. The CDC recommends that animal parks provide adequate hand washing stations and post guidelines telling visitors to wash their hands after leaving animal areas. Anna drinks plenty of fluids and recovers in 5 days.

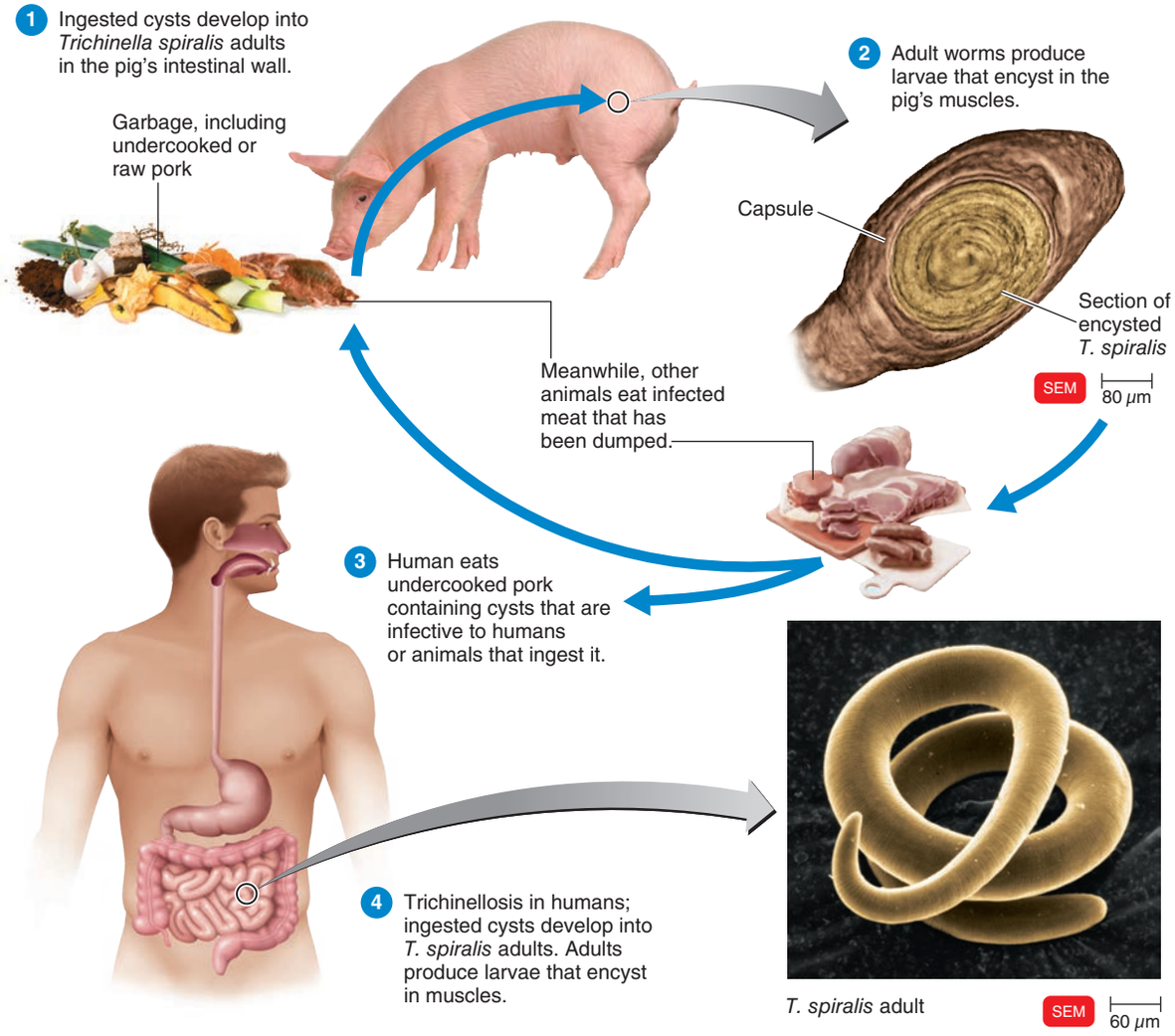


Figure 25.25 The life cycle of *Trichinella spiralis*, the causative agent of trichinellosis.

Q What is the most common vehicle of infection of *T. spiralis*?

Trichinellosis

Most infections by the small roundworm *Trichinella spiralis*, called **trichinellosis** (formerly called *trichinosis*), are insignificant. The larvae, in encysted form, are located in muscles of the host. In 1970, routine autopsies of human diaphragm muscles showed that about 4% of cadavers tested carried this parasite.

The severity of the disease is generally proportional to the number of larvae ingested. Ingesting undercooked pork is probably the most common mode of infection (Figure 25.25), but eating the flesh of animals that feed on garbage (bears, for example) is an increasing cause of outbreaks. Quite a few human cases of trichinellosis have occurred in France from horsemeat infected in the United States and exported to restaurants. Severe cases can be fatal—sometimes in only a few days.

Any ground meat can be contaminated from machinery previously used to grind contaminated meats. Eating raw sausage or hamburger is a risky habit. One person acquired trichinellosis by chewing their fingernails after handling infected pork. Freezing pork for prolonged periods (for example, −23°C for 10 days) kills *T. spiralis*. However, freezing doesn't kill some species found in wild game, such as *Trichinella nativa*.

In the muscles of intermediate hosts such as pigs, the *T. spiralis* larvae are encysted in the form of short worms about 1 mm in length. When a human ingests the flesh of an infected animal, digestive action in the intestine removes the cyst wall. The organism then matures into the adult form. The adult worms spend only about a week in the intestinal mucosa and produce larvae that invade tissue. Eventually, the encysted larvae localize in muscle (common sites include the diaphragm and eye muscles), where they are barely visible in biopsied specimens.

Symptoms of trichinellosis include fever, swelling around the eyes, and gastrointestinal upset. Small hemorrhages under

the fingernails are often observed. Biopsy specimens, as well as a number of serological tests, can be used in diagnosis. A serological ELISA test that detects the parasite in meats has been developed. Treatment consists of administering albendazole or mebendazole to kill intestinal worms and corticosteroids to reduce inflammation.

In the past 10 years, the number of cases reported annually in the United States has varied from 16 to 129. Death is extremely rare.

Study Outline

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Introduction (p. 707)

1. Diseases of the digestive system are the second most common illnesses in the United States.
2. Diseases of the digestive system usually result from ingesting microorganisms or their toxins in food and water.
3. The fecal–oral cycle of transmission can be broken by the proper disposal of sewage, the disinfection of drinking water, and proper food preparation and storage.

Structure and Function of the Digestive System (p. 708)

1. The gastrointestinal (GI) tract, or alimentary canal, consists of the mouth, pharynx, esophagus, stomach, small intestine, and large intestine.
2. In the GI tract, with mechanical and chemical help from the accessory structures, large food molecules are broken down into smaller molecules that can be transported by blood or lymph to cells.
3. Feces, the solids resulting from digestion, are eliminated through the anus.
4. GALT is part of the immune system.

Normal Microbiota of the Digestive System (pp. 708–709)

1. Large numbers of bacteria colonize the mouth.
2. The stomach and small intestine have few resident microorganisms.
3. Bacteria in the large intestine assist in degrading food and synthesizing vitamins.
4. Up to 40% of fecal mass is microbial cells.

Bacterial Diseases of the Mouth (pp. 709–712)

Dental Caries (Tooth Decay) (pp. 709–711)

1. Dental caries begin when tooth enamel and dentin are eroded and the pulp is exposed to bacterial infection.
2. *Streptococcus mutans,* found in the mouth, uses sucrose to form dextran from glucose and lactic acid from fructose.
3. Bacteria adhere to teeth by the sticky dextran, forming dental plaque.
4. Acid produced during carbohydrate fermentation destroys tooth enamel at the site of the plaque.
5. Gram-positive rods and filamentous bacteria can penetrate into dentin and pulp.
6. Carbohydrates such as starch, mannitol, sorbitol, and xylitol are not used by cariogenic bacteria to produce dextran and do not promote tooth decay.
7. Caries are prevented by restricting the ingestion of sucrose and by the physical removal of plaque.

Periodontal Disease (pp. 711–712)

8. Caries of the cementum and gingivitis are caused by streptococci, actinomycetes, and anaerobic gram-negative bacteria.
9. Chronic gum disease (periodontitis) can cause bone destruction and tooth loss; periodontitis is due to an inflammatory response to a variety of bacteria growing on the gums.
10. Acute necrotizing ulcerative gingivitis is often caused by *Prevotella intermedia.*

Bacterial Diseases of the Lower Digestive System (pp. 712–724)

1. A gastrointestinal infection is caused by the growth of a pathogen in the intestines.
2. Incubation times range from 12 hours to 2 weeks. Symptoms of infection generally include a fever.
3. A bacterial intoxication results from ingesting preformed bacterial toxins.
4. Symptoms appear 1 to 48 hours after ingestion of the toxin. Fever is not usually a symptom of intoxication.
5. Infections and intoxications cause diarrhea, dysentery, or gastroenteritis.
6. These conditions are usually treated with fluid and electrolyte replacement.

Staphylococcal Food Poisoning (Staphylococcal Enterotoxicosis) (pp. 713–714)

7. Staphylococcal food poisoning is caused by the ingestion of an enterotoxin produced in improperly stored foods.
8. *S. aureus* is inoculated into foods during preparation. The bacteria grow and produce enterotoxin in food stored at room temperature.
9. Boiling for 30 minutes is not sufficient to denature the exotoxin.
10. Foods with high osmotic pressure and those not cooked immediately before consumption are most often the source of staphylococcal enterotoxicosis.
11. Laboratory identification of *S. aureus* isolated from foods is used to trace the source of contamination.

Shigellosis (Bacillary Dysentery) (pp. 714–715)

12. Shigellosis is caused by any of four species of *Shigella.*
13. Symptoms include blood and mucus in stools, abdominal cramps, and fever. Infections by *S. dysenteriae* result in ulceration of the intestinal mucosa.

Salmonellosis (*Salmonella* Gastroenteritis) (pp. 715–716)

14. Salmonellosis, or *Salmonella* gastroenteritis, is caused by many *Salmonella enterica* serovars.
15. Symptoms include nausea, abdominal pain, and diarrhea and begin 12 to 36 hours after eating large numbers of *Salmonella.* Septic shock can occur in infants and in the elderly.
16. Mortality is lower than 1%, and recovery can result in a carrier state.
17. Cooking food will usually kill *Salmonella.*

Typhoid Fever (pp. 716–717)

18. *Salmonella typhi* causes typhoid fever; the bacteria are transmitted by contact with human feces.
19. Fever and malaise occur after a 2-week incubation period. Symptoms last 2 to 3 weeks.
20. *S. typhi* is harbored in the gallbladder of carriers.
21. Typhoid fever is treated with quinolones and cephalosporins; vaccines are available for high-risk people.

Cholera (pp. 717–718)

22. *Vibrio cholerae* O:1 and O:139 produce an exotoxin that alters the membrane permeability of the intestinal mucosa; the resulting vomiting and diarrhea cause loss of body fluids.
23. The symptoms last for a few days. Untreated cholera has a 50% mortality rate.

Noncholera Vibrios (pp. 718–719)

24. Ingestion of other *V. cholerae* serotypes can result in mild diarrhea.
25. *Vibrio* gastroenteritis can be caused by *V. parahaemolyticus.*
26. These diseases are contracted by eating contaminated crustaceans or contaminated mollusks.

Escherichia coli Gastroenteritis (pp. 719–722)

27. Enterotoxigenic, enteroinvasive, and enteroaggregative strains of *E. coli* cause diarrhea.
28. Enterohemorrhagic *E. coli,* such as *E. coli* O157:H7, produces Shiga toxins that cause inflammation and bleeding of the colon, including hemorrhagic colitis and hemolytic uremic syndrome.
29. The most common causes of traveler's diarrhea are enterotoxigenic and enteroaggregative *E. coli*.

Campylobacter Gastroenteritis (p. 722)

30. *Campylobacter* is the second most common cause of diarrhea in the United States.
31. *Campylobacter* is transmitted in cow's milk.

Helicobacter Peptic Ulcer Disease (pp. 722–723)

32. *Helicobacter pylori* produces ammonia, which neutralizes stomach acid; the bacteria colonize the stomach mucosa and cause peptic ulcer disease.
33. Bismuth and several antibiotics may be useful in treating peptic ulcer disease.

Yersinia Gastroenteritis (p. 723)

34. *Y. enterocolitica* and *Y. pseudotuberculosis* are transmitted in meat and milk.
35. *Yersinia* can grow at refrigeration temperatures.

Clostridium perfringens Gastroenteritis (pp. 723–724)

36. *C. perfringens* causes a self-limiting gastroenteritis.
37. Endospores survive heating and germinate when foods (usually meats) are stored at room temperature.
38. Exotoxin produced when the bacteria grow in the intestines is responsible for the symptoms.
39. Diagnosis is based on isolating and identifying the bacteria in stool samples.

Clostridium difficile–Associated Diarrhea (p. 724)

40. Growth of *C. difficile* following antibiotic therapy can result in mild diarrhea or colitis.
41. The condition is usually associated with health care environments and day care centers.

Bacillus cereus Gastroenteritis (p. 724)

42. Ingesting food contaminated with the soil saprophyte *Bacillus cereus* can result in diarrhea, nausea, and vomiting.

Viral Diseases of the Digestive System (pp. 724–732)

Mumps (pp. 724–725)

1. Mumps virus enters and exits the body through the respiratory tract.
2. About 16 to 18 days after exposure, the virus causes inflammation of the parotid glands, fever, and pain during swallowing. About 4 to 7 days later, orchitis may occur.
3. After onset of the symptoms, the virus is found in the blood, saliva, and urine.
4. A measles, mumps, rubella (MMR) vaccine is available.

Hepatitis (pp. 725–731)

5. Inflammation of the liver is called hepatitis. Symptoms include loss of appetite, malaise, fever, and jaundice.
6. Viral causes of hepatitis include hepatitis viruses, Epstein-Barr virus (EBV), and cytomegalovirus (CMV).
7. Hepatitis A virus (HAV) causes hepatitis A; at least 50% of all cases are subclinical.
8. Hepatitis B virus (HBV) causes hepatitis B, which is frequently serious.
9. Hepatitis C virus (HCV) is transmitted via blood.
10. Hepatitis D virus (HDV) occurs as a superinfection or coinfection with hepatitis B virus.
11. Hepatitis E virus (HEV) is spread by the fecal–oral route.

Viral Gastroenteritis (pp. 731–732)

12. Viral gastroenteritis is most often caused by a *Rotavirus* or *Norovirus*.
13. The incubation period is 2 to 3 days; diarrhea lasts up to 1 week.

Fungal Diseases of the Digestive System (pp. 732–733)

1. Mycotoxins are toxins produced by some fungi.
2. Mycotoxins affect the blood, nervous system, kidneys, or liver.

3. Cereal grains are the crop most often contaminated with the *Claviceps* mycotoxin.
4. Peanuts are the crop most often contaminated with aflatoxin-producing *Aspergillus flavus*.

Protozoan Diseases of the Digestive System (pp. 733–735)

Giardiasis (pp. 733–734)

1. *Giardia intestinalis* grows in the intestines of humans and wild animals and is transmitted in contaminated water.
2. Symptoms of giardiasis are malaise, nausea, flatulence, weakness, and abdominal cramps that persist for weeks.

Cryptosporidiosis (pp. 734–735)

3. *Crytosporidium* spp. cause diarrhea; in immunosuppressed patients, the disease is prolonged for months.
4. The pathogen is transmitted in contaminated water.

Cyclospora Diarrheal Infection (p. 735)

5. *Cyclospora cayetanensis* causes diarrhea; the protozoan was first identified in 1993.
6. It is transmitted in contaminated produce.

Amebic Dysentery (Amebiasis) (p. 735)

7. Amebic dysentery is caused by *Entamoeba histolytica* growing in the large intestine.
8. The ameba feeds on red blood cells and GI tract tissues. Severe infections result in abscesses.

Helminthic Diseases of the Digestive System (pp. 735–741)

Tapeworms (p. 736)

1. Tapeworms are contracted by the consumption of undercooked beef, pork, or fish containing encysted larvae (cysticerci).
2. The scolex attaches to the intestinal mucosa of humans (the definitive host) and matures into an adult tapeworm.
3. Eggs are shed in the feces and must be ingested by an intermediate host.
4. Adult tapeworms can be undiagnosed in a human.
5. Neurocysticercosis in humans occurs when the pork tapeworm larvae encyst in humans.

Hydatid Disease (pp. 736–738)

6. Humans infected with the tapeworm *Echinococcus granulosus* might have hydatid cysts in their lungs or other organs.
7. Dogs and wolves are usually the definitive hosts, and sheep or deer are the intermediate hosts for *E. granulosus.*

Nematodes (pp. 738–741)

8. Humans are the definitive host for pinworms, *Enterobius vermicularis.*
9. Hookworm larvae bore through skin and migrate to the intestine to mature into adults.
10. *Ascaris lumbricoides* adults live in human intestines.
11. Ingested *Trichuris trichiura* eggs hatch in the large intestine. Larvae live attached to the intestinal lining.
12. *Trichinella spiralis* larvae encyst in muscles of humans and other mammals to cause trichinellosis.

Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

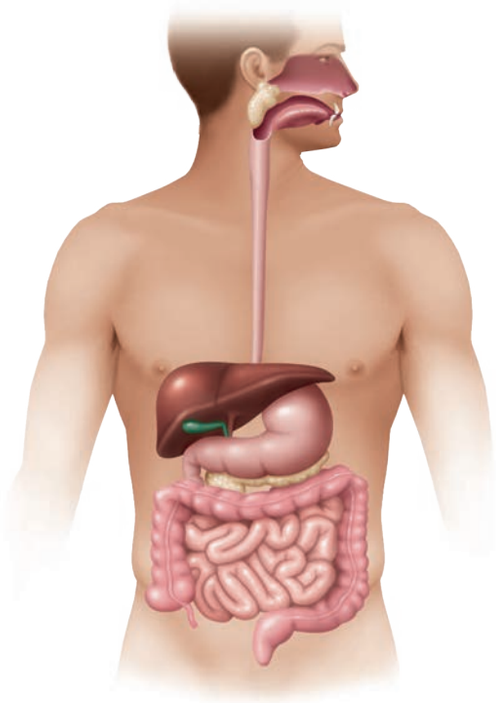
1. Complete the following table:

Disease	Causative Agent	Method of Transmission	Symptoms	Treatment
Aflatoxin poisoning				
Cryptosporidiosis				
Pinworms				
Whipworms				

2. Complete the following table:

Causative Agent	Suspect Foods	Treatment	Prevention
Vibrio parahaemolyticus			
V. cholerae			
E. coli O157			
Campylobacter jejuni			
Yersinia enterocolitica			
Clostridium perfringens			
Bacillus cereus			
Staphylococcus aureus			
Salmonella enterica			
Shigella spp.			

3. DRAW IT Identify the site colonized by the following organisms: *Echinococcus granulosus, Enterobius vermicularis, Giardia, Helicobacter pylori,* hepatitis B virus, mumps virus, rotavirus, *Salmonella, Shigella, Streptococcus mutans, Trichinella spiralis, Trichuris.*



4. *E. coli* is part of the normal microbiota of the intestines and can cause gastroenteritis. Explain why this one bacterial species is both beneficial and harmful.
5. Define *mycotoxin.* Give an example of a mycotoxin.
6. Explain how the following diseases differ and how they are similar: giardiasis, amebic dysentery, *Cyclospora* diarrheal infection, and cryptosporidiosis.
7. Differentiate among the following factors of bacterial intoxication and bacterial infection: prerequisite conditions, causative agents, onset, duration of symptoms, and treatment.
8. Complete the following table:

Disease	Causative Agent	Mode of Transmission	Site of Infection	Symptoms	Prevention
Mumps					
Hepatitis A					
Hepatitis B					
Viral gastro-enteritis					

9. Look at life cycle diagrams for human tapeworm and trichinellosis. Indicate stages in the life cycles that could be easily broken to prevent these diseases.
10. NAME IT Cysts of this flagellated organism survive in water; when ingested, the trophozoite grows in the intestine, causing diarrhea.

Multiple Choice

1. All of the following can be transmitted by recreational (i.e., swimming) water sources *except*
   a. amebic dysentery.
   b. cholera.
   c. giardiasis.
   d. hepatitis B.
   e. salmonellosis.
2. A patient with nausea, vomiting, and diarrhea within 5 hours after eating most likely has
   a. shigellosis.
   b. cholera.
   c. *E. coli* gastroenteritis.
   d. salmonellosis.
   e. staphylococcal food poisoning.
3. Isolation of *E. coli* from a stool sample is diagnostic proof that the patient has
   a. cholera.
   b. *E. coli* gastroenteritis.
   c. salmonellosis.
   d. typhoid fever.
   e. none of the above
4. Gastric ulcers are caused by
   a. stomach acid.
   b. *Helicobacter pylori.*
   c. spicy food.
   d. acidic food.
   e. stress.
5. Microscopic examination of a patient's fecal culture shows comma-shaped bacteria. These bacteria require 2–4% NaCl to grow. The bacteria probably belong to the genus
   a. *Campylobacter.*
   b. *Escherichia.*
   c. *Salmonella.*
   d. *Shigella.*
   e. *Vibrio.*
6. A cholera epidemic in Peru had all of the following characteristics. Which one *led* to the others?
   a. eating raw fish
   b. sewage contamination of water
   c. catching fish in contaminated water
   d. *Vibrio* in fish intestine
   e. including fish intestines with edibles

Use the following choices to answer questions 7–10:

   a. *Campylobacter*
   b. *Cryptosporidium*
   c. *Escherichia*
   d. *Salmonella*
   e. *Trichinella*

7. Identification is based on the observation of oocysts in feces.
8. A characteristic disease symptom caused by this microorganism is swelling around the eyes.
9. Microscopic observation of a stool sample reveals gram-negative helical cells.
10. This microbe is frequently transmitted to humans via raw eggs.

Analysis

1. Why is a human infection of *Trichinella* considered a dead-end for the parasite?
2. Complete the following table:

Disease	Conditions Necessary for Microbial Growth	Basis for Diagnosis	Prevention
Staphylococcal food poisoning			
Salmonellosis			
C. difficile diarrhea			

3. Match the foods in column A with the microorganism (column B) most likely to contaminate each:

Column A	Column B
_____ a. Beef	1. *Vibrio*
_____ b. Delicatessen meats	2. *Campylobacter*
_____ c. Chicken	3. *E. coli* O157:H7
_____ d. Milk	4. *Listeria*
_____ e. Oysters	5. *Salmonella*
_____ f. Pork	6. *Trichinella*

   What disease does each microbe cause? How can these diseases be prevented?
4. Which diseases of the gastrointestinal tract can be acquired by swimming in a pool or lake? Why are these diseases not likely to be acquired while swimming in the ocean?

Clinical Applications and Evaluation

1. In New York on April 26, patient A was hospitalized with a 2-day history of diarrhea. An investigation revealed that patient B had onset of watery diarrhea on April 22. On April 24, three other people (patients C, D, and E) had onset of diarrhea. All three had vibriocidal antibody titers ≥ 640. In Ecuador on April 20, B bought crabs that were boiled and shelled. He shared crabmeat with two people (F and G), then froze the remaining crab in a bag. Patient A returned to New York on April 21 with the bag of crabmeat in his suitcase. The bag was placed in a freezer overnight and thawed on April 22 in a double-boiler for 20 minutes. The crab was served 2 hours later in a crab salad. The crab was consumed during a 6-hour period by A, C, D, and E. Individuals F and G did not become ill. What is the etiology of this disease? How was it transmitted, and how could it have been prevented?
2. The 2130 students and employees of a public school system developed diarrheal illness on April 2. The cafeteria served chicken that day. On April 1, part of the chicken was placed in water-filled pans and cooked in an oven for 2 hours at a dial setting of 177°C. The oven was turned off, and the chicken was left overnight in the warm oven. The remainder of the chicken was cooked for 2 hours in a steam cooker and then left in the device overnight at the lowest possible setting (43°C). Two serotypes of a gram-negative, cytochrome oxidase-negative, lactose-negative rods were isolated from 32 patients. What is the pathogen? How could this outbreak have been prevented?
3. A 31-year-old man became feverish 4 days after arriving at a vacation resort in Idaho. During his stay, he ate at two restaurants that were not associated with the resort. At the resort, he drank soft drinks with ice, used the hot tub, and went fishing. The resort is supplied by a well that was dug 3 years ago. He went to the hospital when he developed vomiting and bloody diarrhea. Gram-negative, lactose-negative bacteria were cultured from his stool. The patient recovered after receiving intravenous fluids. What microorganism most likely caused his symptoms? How is this disease transmitted? What is the most likely source of his infection, and how would you verify the source?
4. Three to 5 days after eating Thanksgiving dinner at a restaurant, 112 people developed fever and gastroenteritis. All the food had been consumed except for five "doggie" bags. Bacterial analysis of the mixed contents of the bags (containing roast turkey, giblet gravy, and mashed potatoes) showed the same bacterium that was isolated from the patients. The gravy had been prepared from giblets of 43 turkeys that had been refrigerated for 3 days prior to preparation. The uncooked giblets were ground in a blender and added to a thickened hot stock mixture. The gravy was not reboiled and was stored at room temperature throughout Thanksgiving Day. What was the source of the illness? What was the most likely etiologic agent? Was this an infection or an intoxication?



In the Clinic

You are a nurse in a community sexual health clinic. Your first patient today is Kylin, a 20-year-old college student who dropped in for her first pelvic exam. She has had two sexual partners in the past year. She has not noticed vaginal discharge, sores, or painful urination. During her pelvic examination, you observe that her cervix appears inflamed and that a watery discharge is present. **What are the most likely microbial infections? What laboratory tests would confirm a diagnosis?**

Hint: Read about bacterial diseases of the reproductive systems on pages 751–762.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

26

Microbial Diseases of the Urinary and Reproductive Systems

The **urinary system** is composed of organs that regulate the chemical composition and volume of the blood and as a result excrete mostly nitrogenous waste products and water. Because it provides an opening to the outside environment, the urinary system is prone to infections from external contacts. The mucosal membranes that line the urinary system are moist and, compared to skin, more supportive of bacterial growth. The *Leptospira interrogans* bacteria shown in the photo infect the kidneys (leptospirosis) but enter through a cut or mucous membranes of the nose or mouth. Leptospirosis is the subject of the Clinical Case in this chapter.

The **reproductive system** shares several of the organs with the urinary system. Its function is to produce gametes that propagate the species and, in the female, to support and nourish the developing embryo and fetus. In the same fashion as the urinary system, it provides openings to the external environment and is therefore prone to infections. This is especially true because intimate sexual contact can promote exchange of microbial pathogens between individuals. It isn't surprising, therefore, that certain pathogens have adapted to this environment and a sexual mode of transmission. As a result, they are often no longer able to survive in more rigorous environments.

Leptospira interrogans.

Structure and Function of the Urinary System

LEARNING OBJECTIVE

26-1 List the antimicrobial features of the urinary system.

The **urinary system** consists of two *kidneys,* two *ureters,* a single *urinary bladder,* and a single *urethra* (Figure 26.1). Certain wastes, collectively called *urine,* are removed from the blood as it circulates through the kidneys. The urine passes through the ureters into the urinary bladder, where it is stored prior to elimination from the body through the urethra. In the female, the urethra conveys only urine to the exterior. In the male, the urethra is a common tube for both urine and seminal fluid.

Where the ureters enter the urinary bladder, physiological valves prevent the backflow of urine to the kidneys. This mechanism helps shield the kidneys from lower urinary tract infections. In addition, normal urine has some antimicrobial properties. The flushing action of urine during urination also tends to remove potentially infectious microbes.

CHECK YOUR UNDERSTANDING

Does the pH of urine facilitate the growth of most bacteria? **26-1**

Structure and Function of the Reproductive Systems

LEARNING OBJECTIVE

26-2 Identify the portals of entry for microbes into the female and male reproductive systems.

The **female reproductive system** consists of two *ovaries,* two *uterine (fallopian) tubes,* the *uterus,* including the *cervix,* the *vagina,* and *external genitals* (Figure 26.2). The ovaries produce female sex hormones and ova (eggs). When an ovum is released during the process of ovulation, it enters a uterine tube, where fertilization may occur if viable sperm are present. The fertilized ovum (zygote) descends the tube and enters the uterus. It implants in the inner wall of the uterus and remains there while it develops into an embryo and, later, a fetus. The external genitals (*vulva*) include the clitoris, labia, and glands that produce a lubricating secretion during copulation.

The **male reproductive system** consists of two *testes,* a system of *ducts, accessory glands,* and the *penis* (Figure 26.3). The testes produce male sex hormones and sperm. To exit the body, sperm cells pass through a series of ducts: the epididymis, ductus (vas) deferens, ejaculatory duct, and urethra.

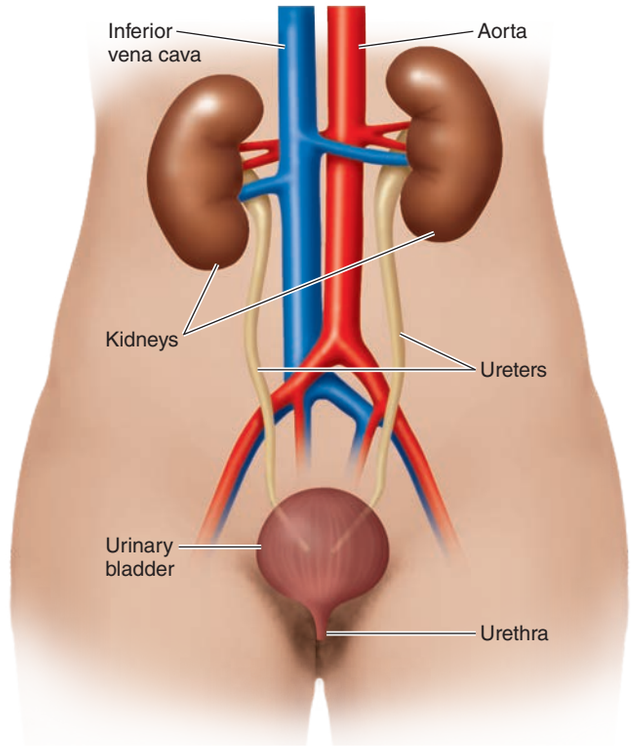


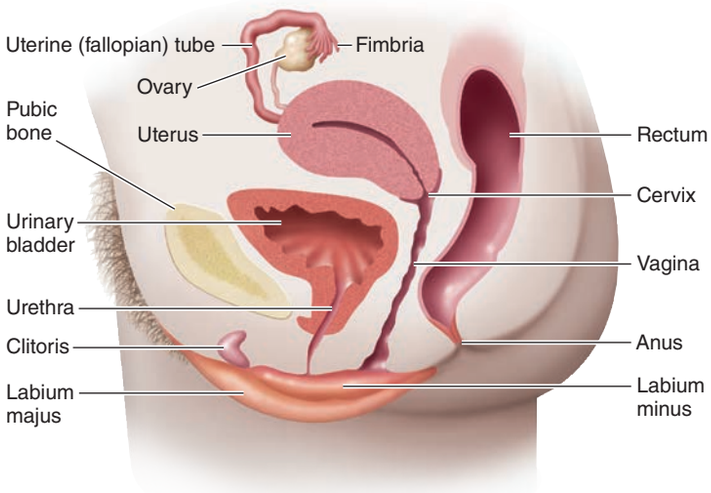
Figure 26.1 Organs of the human urinary system, shown here in the female.

What features of the urinary system help prevent colonization by microbes?

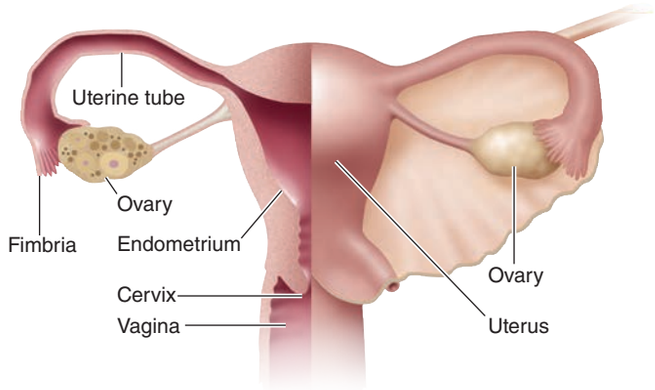
Clinical Case: Swimming Upstream

Maricel Quimuyog, a 25-year-old professional freestyle kayaker, is having difficulties training for her next kayaking event. Although Maricel normally enjoys her outdoor activities and is in good physical shape, she hasn't been feeling well. Thinking at first her headache, fever, and muscle pain are simply the flu, Maricel tries to take it easy. But when her skin and the whites of her eyes start to look jaundiced and she has trouble catching her breath, Maricel becomes concerned and goes to her physician. On physical examination, Maricel is alert and her lungs are clear. Her physician sends blood and urine samples to a local laboratory for blood counts and cultures; the blood count shows 9500 leukocytes/mm^3 (88% neutrophils, 10% lymphocytes, and 2% monocytes). Maricel's 24-hour urine output, however, is nearly double the normal amount. Maricel's physician is concerned because of the dehydration and loss of sodium and magnesium in the urine.

What is causing Maricel's symptoms? Read on to find out.



(a) Side view section of female pelvis showing reproductive organs



(b) Front view of female reproductive organs, with the uterine tube and ovary to the left in the drawing sectioned. The fimbriae move to create fluid movement that moves the egg into the uterine tube.

Figure 26.2 Female reproductive organs.

Q Where are normal microbiota found in the female reproductive system?

CHECK YOUR UNDERSTANDING

Look at Figure 26.2. Is a microbe entering the female reproductive system (the uterus, etc.) necessarily also entering the bladder, causing cystitis? **26-2**

Normal Microbiota of the Urinary and Reproductive Systems

LEARNING OBJECTIVE

26-3 Describe the normal microbiota of the upper urinary tract, the male urethra, and the female urethra and vagina.

Normal urine is sterile, but it may become contaminated with microbiota of the skin near the end of its passage through the urethra. Therefore, urine collected directly from the urinary bladder has fewer microbial contaminants than voided urine.

The predominant bacteria in the vagina are the lactobacilli. These bacteria produce lactic acid, which maintains the acidic pH (3.8 to 4.5) of the vagina, inhibiting the growth of most other microbes. Most vaginal lactobacilli produce hydrogen peroxide, which also inhibits growth of other bacteria. Estrogens (sex hormones) promote the growth of lactobacilli by enhancing the production of glycogen by vaginal epithelial cells. The glycogen quickly breaks down into glucose, which the lactobacilli metabolize into lactic acid.

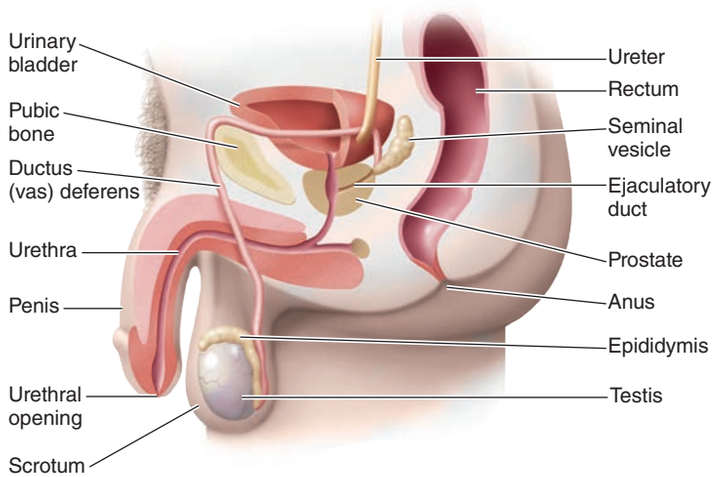
Other bacteria, such as streptococci, various anaerobes, and some gram-negatives, are also found in the vagina. The yeastlike fungus *Candida albicans* (see page 765) is part of the normal microbiota of 10–25% of women, even when they are asymptomatic.

Pregnancy and menopause are often associated with higher rates of urinary tract infections. The reason is that estrogen levels are lower, resulting in lower populations of lactobacilli and therefore less vaginal acidity.

The male urethra is usually sterile, except for a few contaminating microbes near the external opening.

CHECK YOUR UNDERSTANDING

What is the association between estrogens and the microbiota of the vagina? **26-3**



Side view section of male pelvis

Figure 26.3 Male reproductive and urinary organs. A side view section of a male pelvis.

Q What factors protect the male urinary and reproductive systems from infection?

Diseases of the Urinary System

The urinary system normally contains few microbes, but it's subject to opportunistic infections that can be quite troublesome. Almost all such infections are bacterial, although occasional infections by schistosome parasites, protozoa, and fungi occur. In addition, as we will see in this chapter, sexually transmitted diseases often affect the urinary system as well as the reproductive system.

Bacterial Diseases of the Urinary System

LEARNING OBJECTIVES

26-4 Describe the modes of transmission for urinary and reproductive system infections.

26-5 List the microorganisms that cause cystitis, pyelonephritis, and leptospirosis, and name the predisposing factors for these diseases.

Urinary system infections are most frequently initiated by an inflammation of the urethra, or *urethritis.* Infection of the urinary bladder is called *cystitis,* and infection of the ureters is *ureteritis.* The most significant danger from lower urinary tract infections is that they may move up the ureters and affect the kidneys, causing *pyelonephritis.* Occasionally the kidneys are affected by systemic bacterial diseases, such as *leptospirosis.* The pathogens causing these diseases are found in excreted urine.

Bacterial infections of the urinary system are usually caused by microbes that enter the system from external sources. In the United States, about 7 million urinary tract infections occur each year. About 900,000 cases are healthcare-associated, and probably 90% of these are associated with urinary catheters. Because of the proximity of the anus to the urinary opening, intestinal bacteria predominate in urinary tract infections. Most infections of the urinary tract are caused by *Escherichia coli.* Infections by *Pseudomonas,* because of their natural resistance to antibiotics, are especially troublesome.

Diseases of the urinary system are summarized in Diseases in Focus 26.1.

Cystitis

Cystitis is a common inflammation of the urinary bladder in females. Symptoms often include *dysuria* (difficult, painful, urgent urination) and pyuria.

The female urethra is less than 2 inches long, and microorganisms traverse it readily. It's also closer than the male urethra to the anal opening and its contaminating intestinal bacteria. These considerations are reflected in the fact that the rate of urinary tract infections in women is eight times that of men. In either gender, most cases are due to infection by *E. coli,* which can be identified by cultivation on differential media such as MacConkey's agar. Another frequent bacterial cause is the coagulase-negative *Staphylococcus saprophyticus* (STAF-i-lō-kok′kus sa-PRŌ-fi′ti′-kus).

As a general rule, a urine sample with more than 100 colony forming units (CFU) per milliliter of potential pathogens (such as coliforms) from a female patient with cystitis is considered significant. The diagnosis should also include a positive urine test for *leukocyte esterase* (LE), an enzyme produced by neutrophils—which indicates an active infection. Trimethoprim-sulfamethoxazole usually clears cases of cystitis quickly. Fluoroquinolone antibiotics or ampicillin are often successful if drug resistance is encountered.

Pyelonephritis

In 25% of untreated cases, cystitis may progress to **pyelonephritis,** an inflammation of one or both kidneys. Symptoms are fever and flank or back pain. In females, it's often a complication of lower urinary tract infections. The causative agent in about 75% of the cases is *E. coli.* Pyelonephritis generally results in bacteremia; blood cultures and a Gram stain of the urine for bacteria are useful for diagnosis. A urine sample of more than 10,000 CFUs/ml and a positive LE test indicate pyelonephritis. If pyelonephritis becomes chronic, scar tissue forms in the kidneys and severely impairs their function. Because pyelonephritis is a potentially life-threatening condition, treatment usually begins with intravenous, extended term administration of a broad-spectrum antibiotic, such as a second- or third-generation cephalosporin.

Leptospirosis

Leptospirosis is primarily a disease of domestic or wild animals, but it can be passed to humans and sometimes causes severe kidney or liver disease. The causative agent is the spirochete *Leptospira interrogans* (in-TER-ah-ganz′), shown in **Figure 26.4**. *Leptospira* has a characteristic shape: an exceedingly fine spiral, only about 0.1 μm in diameter, wound so tightly that it is barely discernible under a darkfield microscope. Like other spirochetes, *L. interrogans* (so named because the hooked ends suggest a question mark) stains poorly and is difficult to see under a normal light microscope. It's an obligate aerobe that can be grown in a variety of artificial media supplemented with rabbit serum.

Animals infected with the spirochete shed the bacteria in their urine for extended periods. In rats, the bacteria inhabit renal tubules, an immunologically privileged site, where they continue to reproduce and are shed, copiously, in urine for

DISEASES IN FOCUS 26.1

Bacterial Diseases of the Urinary System

A 20-year-old woman feels a stinging sensation when urinating and feels an urgent need to urinate, even if very little urine is excreted. Lactose-fermenting, gram-negative rods are cultured from her urine (see the photo). Use the table below to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology



MacConkey agar culture from the patient's urine. Designed to selectively grow gram-negative bacteria and differentiate them by their ability to ferment lactose.

Disease	Pathogen	Symptoms	Diagnosis	Treatment
Cystitis (urinary bladder infection)	*Escherichia coli, Staphylococcus saprophyticus*	Difficulty or pain in urination	>100 CFU/ml potential pathogens and + LE test	Trimethoprim-sulfamethoxazole
Pyelonephritis (kidney infection)	Primarily *E. coli*	Fever; back or flank pain	$>10^4$ CFU/ml and + LE test	Cephalosporin
Leptospirosis (kidney infection)	*Leptospira interrogans*	Headaches, muscular aches, fever; kidney failure a possible complication	Serological test	Doxycycline

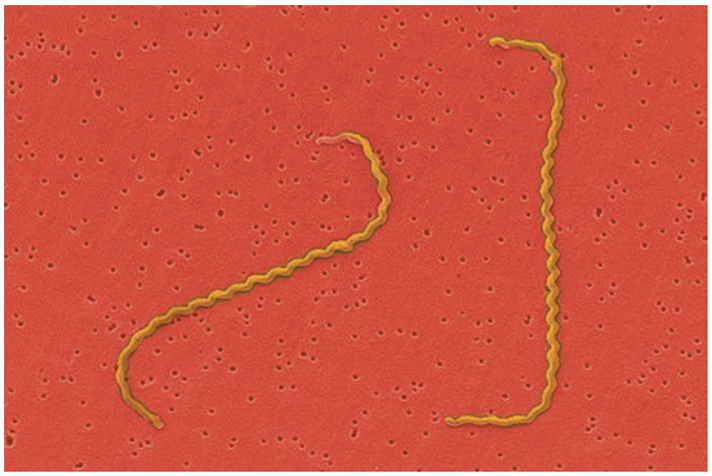


Figure 26.4 *Leptospira interrogans,* the cause of leptospirosis. This photo shows two of these tightly coiled spirochetes.

Q On what basis is *L. interrogans* named?

months. Worldwide, leptospirosis is probably the most common zoonosis; it's endemic in tropical environments, including the state of Hawaii. Humans become infected by contact with urine-contaminated water from freshwater lakes or streams, soil, or sometimes with animal tissue. People whose occupations expose them to animals or animal products are most at risk. Usually the pathogen enters through minor abrasions in the skin or mucous membranes. When ingested, it enters through the mucosa of the upper digestive system. In the United States, dogs and rats are the most common sources. Domestic dogs have a sizable rate of infection; even when immunized, they may continue to shed leptospira.

After an incubation period of 1 to 2 weeks, headaches, muscular aches, chills, and fever abruptly appear. Several days later, the acute symptoms disappear, and the temperature returns to normal. A few days later, however, a second episode of fever may occur. Leptospires are observed within nonphagocytic cells of infected patients. It's uncertain how the pathogens enter host cells, but they use this as a mechanism to spread to target organs and evade the immune system. Because of this, the immune response is delayed long enough (1 or 2 weeks) for the population in the blood and tissues to reach enormous numbers. In a small number of cases the kidneys and liver become seriously infected (*Weil's disease*); kidney failure is the most common cause of death. An emerging form of leptospirosis, *pulmonary hemorrhagic syndrome,* has appeared globally. Affecting the lungs with massive bleeding, it has a fatality rate of more than 50%. Recovery results in a solid immunity, but only to the particular serovar involved. There are usually about 50 cases of Weil's disease reported each year in the United States, but because the clinical symptoms are not distinctive, many cases are probably never diagnosed. A recent study in a clinic serving the urban poor in a large eastern U.S. city found that up to 16% of the patients tested positive for leptospirosis infection.

Most cases of leptospirosis are diagnosed by a serological test that is complicated and usually done by central laboratories. However, a number of rapid serological tests are available for a preliminary diagnosis. Also, a diagnosis can be made by sampling blood, urine, or other fluids for the organism or its DNA. Doxycyline (a tetracycline) is the recommended antibiotic for treatment; however, administration of antibiotics in later stages is often unsatisfactory. That immune reactions are responsible for pathogenesis in this stage may be an explanation.

CHECK YOUR UNDERSTANDING

- Why is urethritis, an infection of the urethra, frequently preliminary to further infections of the urinary tract? **26-4**
- Why is *E. coli* the most common cause of cystitis, especially in females? **26-5**

Clinical Case

Maricel's physician receives the results of her blood and urine cultures. The serological tests for STIs and HIV are negative. In response to her physician's questions about possible travel exposure, Maricel reports that she had been on a 2-week kayaking trip in Costa Rica the previous month. Maricel had really enjoyed the excursion because it included kayaking in streams near isolated rural villages, so she was able to get a feel for the "real" Costa Rica.

What should Maricel's physician test for next?

747 751 755 762

Diseases of the Reproductive Systems

Microbes causing infections of the reproductive systems are usually very sensitive to environmental stresses and require intimate contact for transmission.

Bacterial Diseases of the Reproductive Systems

LEARNING OBJECTIVE

26-6 List the causative agents, symptoms, methods of diagnosis, and treatments for gonorrhea, nongonococcal urethritis (NGU), pelvic inflammatory disease (PID), syphilis, lymphogranuloma venereum (LGV), chancroid, and bacterial vaginosis.

Most diseases of the reproductive systems transmitted by sexual activity have been called **sexually transmitted diseases (STDs).** In recent years there has been a movement to replace this terminology with **sexually transmitted infections (STIs),** a change that is already commonplace in Europe. The reason is that the concept of "disease" implies obvious signs and symptoms. Because many persons infected by the more common sexually transmitted pathogens don't have apparent signs or symptoms, the term *STI* often seems more appropriate and is used in this book. More than 30 bacterial, viral, or parasitic infections have been identified as sexually transmitted. In the United States, over 15 million new cases of STIs are estimated to occur annually. Many of these infections can be successfully treated with antibiotics and can be largely prevented by the use of condoms. For information on new diagnostic options, see the **Big Picture** on STI home kits on pages 752–753.

Gonorrhea

One of the most common reportable, or notifiable, communicable diseases in the United States is **gonorrhea,** an STI caused by the gram-negative diplococcus *Neisseria gonorrhoeae.* An ancient disease, gonorrhea was described and given its present name by the Greek physician Galen in A.D. 150 (*gon* = semen + *rhea* = flow; a flow of semen—apparently, he confused pus with semen). The incidence of gonorrhea has tended to decrease in recent years, but more than 300,000 cases are still reported in the United States each year (**Figure 26.5a**). The true number of cases is probably much larger, probably two or three times those reported (Figure 26.5b). More than 60% of patients with gonorrhea are aged 15 to 24.

To infect, the gonococcus must attach to the mucosal cells of the epithelial wall by means of fimbriae. The pathogen invades the spaces separating columnar epithelial cells, which are found in the oral-pharyngeal area, the eyes, rectum, urethra, opening of the cervix, and the external genitals of prepubertal females. The invasion sets up an inflammation and, when leukocytes move into the inflamed area, the characteristic pus forms. In men, a single unprotected exposure results in infection with gonorrhea 20–35% of the time. Women become infected 60–90% of the time from a single exposure.

Men become aware of a gonorrheal infection by painful urination and a discharge of pus-containing material from the urethra (**Figure 26.6**). About 80% of infected men show these obvious symptoms after an incubation period of only a few days; most others show symptoms in less than a week. In the days before antibiotic therapy, symptoms persisted for weeks. A common complication is urethritis, although this is more likely to be the result of coinfection with *Chlamydia,* which will be

BIG PICTURE

STI Home Test Kits

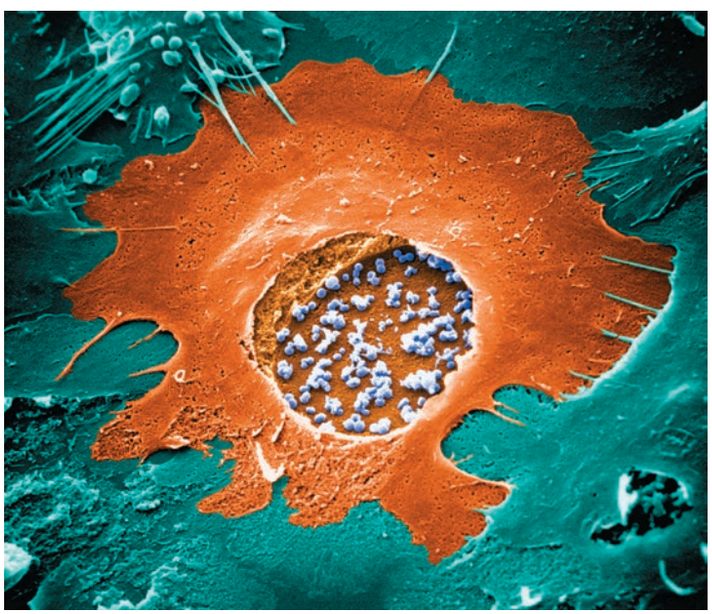
Millions of STI cases go undiagnosed every year. Home test kits can speed diagnosis and treatment, allowing individuals who might otherwise avoid the health clinic to privately begin the screening process.

At-Home Test for Sexually Transmitted Infections

Sexually transmitted infections (STIs) are a major public health concern throughout the world. The Centers for Disease Control and Prevention (CDC) estimates that 2–3 million new cases of chlamydial infections occur annually in the United States—over half of which go undiagnosed.

In the hope of discovering and treating more STIs, researchers at Johns Hopkins School of Medicine created "I Want the Kit," a self-administered screening, currently available free to residents of Maryland, Washington, D.C., and Alaska.

Users collect samples at home and mail them to a lab where nucleic acid amplification testing (NAAT) screens for chlamydial infection, gonorrhea, and trichomoniasis. The user can obtain results in 1–2 weeks using a password over the phone or online. People with positive tests receive referrals to nearby clinics for counseling and treatment options. There is also an option on the website allowing the user to anonymously notify sexual partners that they may also be infected.



Chlamydia **(blue) replicating inside vesicle within a cell**

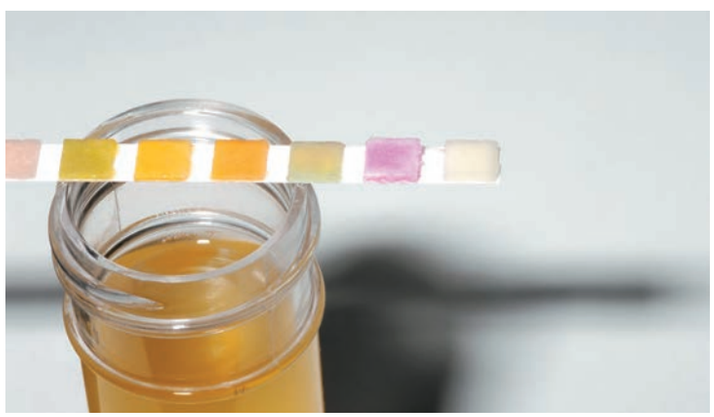


Female test kit contents for "I Want the Kit"

Other Home Test Options for HIV and Urinary Tract Infections

In 2013, the FDA approved OraQuickTM, an HIV oral testing kit. The OraQuick strip is similar to an indirect ELISA test. Priced at about $40 per test, it uses an HIV antigen and enzyme indicator to test the oral mucosa for antibodies against HIV. Clinical studies showed this test produces about one false positive in every 5000 uninfected individuals, and one false negative in every 12 HIV-infected individuals.

While urinary tract infections (UTIs) are not technically STIs, sometimes women misattribute symptoms of an STI as being from a UTI. At-home testing for UTIs is also available. A dipstick is held in the urine stream, and the test strip then indicates presence of nitrites, which are usually produced by bacteria that cause UTIs. These tests also look for presence of leukocytes, which indicate an immune response to an infection.



Uritest, a home test for urinary tract infection

Are At-Home Test Kits a Good Public Health Strategy?

Pros of At-Home Testing

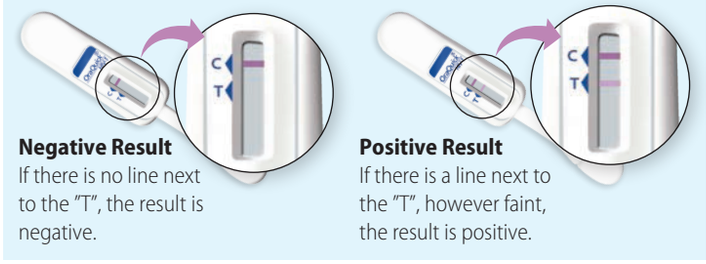
- **More Cases Diagnosed** In a 5-year period, the "I Want the Kit" initiative detected more chlamydial infections than traditional clinics did in the areas where it was available. Its creators estimate that this method of testing would save about $41,000 in direct medical costs per 10,000 women, when compared with clinic-based screening.
- **Better Access for Patients** Home testing kits can also be very helpful for people with limited transportation or for residents of rural areas who live far from medical facilities. Most home test kits are available at drugstores or can be ordered online or over the phone.
- **Quicker Treatment** Providing a screening method that works for people who are reluctant or unable to visit a clinic means more diagnoses and quicker treatment. It can also lead to fewer complications and better prognosis. For example, a positive result from a UTI home test kit may prompt health care providers to prescribe antibiotics without requiring patients to first provide a urine sample for culturing. In this case, faster treatment results in less discomfort and downtime for patients and could prevent a UTI from progressing to a kidney infection.

Some Cons of Home-Testing

Cost Although home test kits reduce public health costs, they increase consumer costs because they are typically not covered by health insurance plans.

Privacy Allowing access to test information through a hotline or website raises concerns that results may fall into the hands of someone other than the patient. People using home kits should be mindful of keeping PINs or other test-related paperwork away from prying eyes.

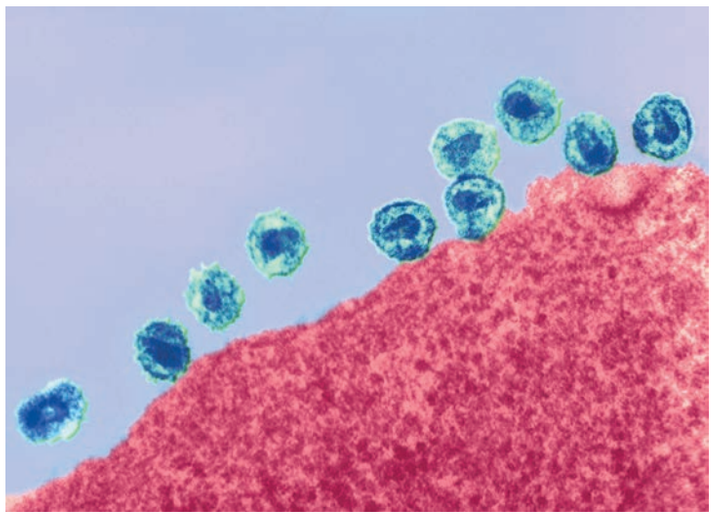
Not All Home Test Kits Are Equally Accurate Unfortunately, not every home test kit sold online today is necessarily effective. Users should seek kits that are FDA approved. And regardless of test results, a person with persistent or worsening symptoms should always see a health care provider.



Negative Result
If there is no line next to the "T", the result is negative.

Positive Result
If there is a line next to the "T", however faint, the result is positive.

A positive OraQuick HIV test contains a synthetic HIV gp-41 protein. If the sample contains antibodies against gp-41, the T strip changes color due to an enzyme reaction.



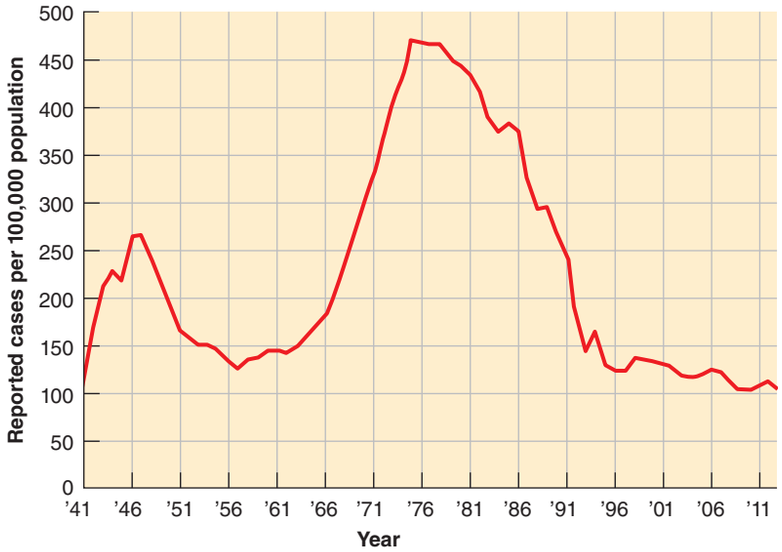
HIVs or human immunodeficiency viruses infecting a cell



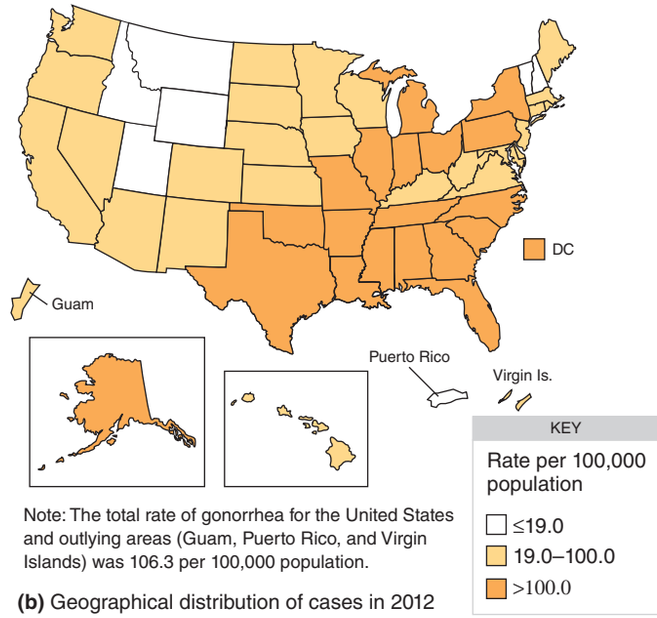
Home screening tests provide an alternative for those without easy access to clinics.

KEY CONCEPTS

- Certain gram-negative organisms convert nitrates to nitrites, so the presence of nitrites in urine can indicate urinary tract infection. **(See Chapter 5, "Anaerobic Respiration," pages 126–127.)**
- Nucleic acid amplification is used to screen for chlamydiasis, gonorrhea, and trichomoniasis infections. **(See Chapter 9, "Polymerase Chain Reaction," pages 243–244.)**
- Some home tests for HIV, such as OraQuick, are similar to indirect ELISA tests. **(See Chapter 18, "Enzyme-Linked Immunosorbent Assay," pages 509–510, and Figures 18.13, 18.14.)**



(a) Incidence of gonorrhea in the United States, 1941–2013



Note: The total rate of gonorrhea for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 106.3 per 100,000 population.

(b) Geographical distribution of cases in 2012

Figure 26.5 The U.S. incidence and distribution of gonorrhea.

Source: CDC, 2014.

Q How do gonococci attach to mucosal epithelial cells?

discussed shortly. An uncommon complication is *epididymitis,* an infection of the epididymis. Usually only unilateral, this is a painful condition resulting from the infection ascending along the urethra and the ductus deferens (see Figure 26.3).

In women, the disease is more insidious. Only the cervix, which contains columnar epithelial cells, is infected. The vaginal walls are composed of stratified squamous epithelial cells, which are not colonized. Very few women are aware of the infection. Later in the course of the disease, there might be abdominal pain from complications such as pelvic inflammatory disease (discussed on page 757).



Figure 26.6 Pus-containing discharge from the urethra of a man with an acute case of gonorrhea.

Q What causes pus formation in gonorrhea?

In both men and women, untreated gonorrhea can disseminate and become a serious, systemic infection. Complications of gonorrhea can involve the joints, heart (*gonorrheal endocarditis*), meninges (*gonorrheal meningitis*), eyes, pharynx, or other parts of the body. *Gonorrheal arthritis,* which is caused by the growth of the gonococcus in fluids in joints, occurs in about 1% of gonorrhea cases. Joints commonly affected include the wrist, knee, and ankle.

If a mother is infected with gonorrhea, the eyes of her infant can become infected as it passes through the birth canal. This condition, **ophthalmia neonatorum,** can result in blindness. Because of the seriousness of this condition and the difficulty of being sure the mother is free of gonorrhea, antibiotics are placed in the eyes of all newborn infants. If the mother is known to be infected, an intramuscular injection of antibiotic is also administered to the infant. Some sort of prophylaxis is required by law in most states. Gonorrheal infections can also be transferred by hand contact from infected sites to the eyes of adults.

Gonorrheal infections can be acquired at any point of sexual contact; pharyngeal and anal gonorrhea are not uncommon. The symptoms of **pharyngeal gonorrhea** often resemble those of the usual septic sore throat. **Anal gonorrhea** can be painful and accompanied by discharges of pus. In most cases, however, the symptoms are limited to itching.

Increased sexual activity with a series of partners, and the fact that in women the disease may go unrecognized, contributed considerably to the increased incidence of gonorrhea and other STIs during the 1960s and 1970s. The widespread use of

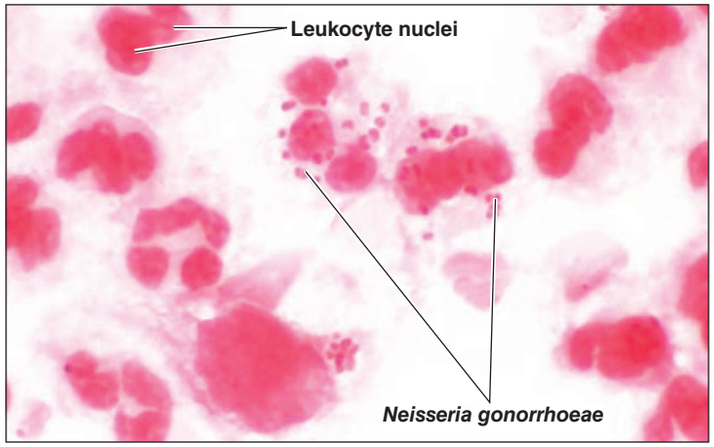


Figure 26.7 A smear of pus from a patient with gonorrhea.
The *Neisseria gonorrhoeae* bacteria are contained within phagocytic leukocytes. These gram-negative bacteria are visible here as pairs of cocci. The large stained bodies are the nuclei of the leukocytes.

How is gonorrhea diagnosed?

oral contraceptives also contributed to the increase. Oral contraceptives often replaced condoms and spermicides, which help prevent disease transmission.

There is no effective adaptive immunity to gonorrhea. The conventional explanation is that the gonococcus exhibits extraordinary antigenic variability—which is true. Lately, though, an alternative theory has appeared that provides an additional mechanism. The gonococcus has certain proteins, Opa proteins (see Chapter 15, page 421), that are essential for it to bind to the cells lining the host's urinary and reproductive tracts. Recent research has shown that an Opa protein variant binds to a certain receptor (CD66) on $CD4^+$ T cells that is needed for activation and proliferation of the cells. This inhibits the development of an immunological memory response against the gonococcus. Almost all clinical isolates of the gonococcus have been found to carry this Opa protein variant. This suppression of immunity may also explain why people with gonorrhea are more susceptible to other STIs, including HIV.

Diagnosis of Gonorrhea

Gonorrhea in men is diagnosed by finding gonococci in a stained smear of pus from the urethra. The typical gram-negative diplococci within the phagocytic leukocytes are readily identified (Figure 26.7). It's uncertain whether these intracellular bacteria are in the process of being killed or whether they survive indefinitely. Probably at least a fraction of the bacterial population remains viable. Gram staining of exudates isn't as reliable with women. Usually, a culture is taken from within the cervix and grown on special media. Cultivation of the nutritionally fastidious bacterium requires an atmosphere enriched in carbon dioxide. The gonococcus is very sensitive to adverse environmental influences (desiccation and temperature) and survives poorly outside the body. It even requires special transporting media to keep it viable for short intervals before the cultivation is under way. Cultivation has the advantage of allowing determination of antibiotic sensitivity.

Diagnosis of gonorrhea has been aided by the development of an ELISA test that detects *N. gonorrhoeae* in urethral pus or on cervical swabs within about 3 hours with high accuracy. This and other rapid tests use monoclonal antibodies against antigens on the surface of the gonococcus. Nucleic acid amplification tests are very accurate for identifying clinical isolates from suspected cases.

Treatment of Gonorrhea

The guidelines for treating gonorrhea require constant revision as resistance appears (See the Clinical Focus box on the next page). For gonorrhea affecting the cervical, urethral, or rectal tissues, the current recommendation is first to use cephalosporins, such as ceftriaxone or cefixime. Ceftriaxone is also recommended for cases of pharyngeal infection. Fluoroquinolones, because resistance to them has developed so rapidly, are no longer recommended. Unless a coinfection by *Chlamydia trachomatis* (see the discussion of nongonococcal urethritis, following) can be ruled out, the patient should also be treated for this organism. It's also standard practice to treat sex partners of patients to decrease the risk of reinfection and to decrease the incidence of STIs in general.

Nongonococcal Urethritis (NGU)

Nongonococcal urethritis (NGU), also known as **nonspecific urethritis (NSU),** refers to any inflammation of the urethra not caused by *Neisseria gonorrhoeae.* Symptoms include painful urination and a watery discharge.

Chlamydia trachomatis

The most common pathogen associated with NGU is *Chlamydia trachomatis.* Many people suffering from gonorrhea are coinfected with *C. trachomatis,* which infects the same columnar

Clinical Case

The physician requests an anti-leptospira antibody test on Maricel's blood. The result is a titer of 1:100, which indicates that Maricel is or has been infected with *Leptospira interrogans* bacteria. Now, at day 15 of Maricel's illness, the physician draws another blood sample for a second microscopic agglutination test. The titer is now 1:800.

Why is a second serological test necessary?

CLINICAL FOCUS

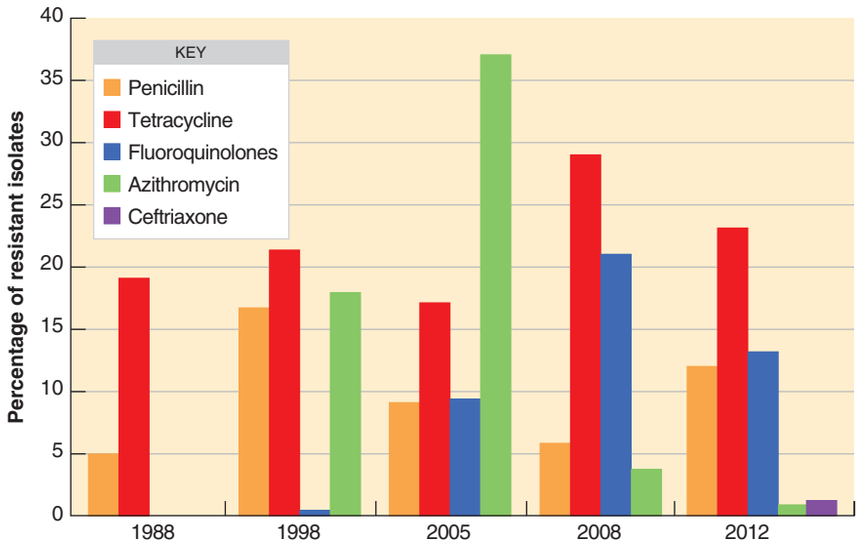
Survival of the Fittest

As you read through this problem, you will see questions that health care providers ask themselves and each other as they solve a clinical problem. Try to answer each question as you read through the problem.

1. On May 24, Jason, a 35-year-old man, goes to the Denver STI Clinic with a history of painful urination and urethral discharge of approximately 1 month's duration.
   What other information do you need about Jason's history?
2. On March 11, Jason returned from a "dating tour" in Thailand, during which he had sexual contact with seven or eight female prostitutes; he denies having had any sexual contact since returning to the United States.
   What sample should be taken, and how should it be tested?
3. *Neisseria gonorrhoeae* is identified by polymerase chain reaction (PCR) of urethral discharge. Jason is treated with a single 500-mg dose of ciprofloxacin orally.
   What is the advantage of PCR or enzyme immunoassay (EIA) over cultures for diagnosis?
4. PCR and EIA provide results within a few hours, eliminating the need for the patient to return for treatment. Jason returns to the clinic on June 7 with continuing symptoms. *N. gonorrhoeae* is again detected in urethral discharge. Jason denies having had any sexual contact since the previous visit. The attending physician requests antimicrobial susceptibility testing of the *N. gonorrhoeae* isolates.
   Why would the physician be interested in antimicrobial susceptibility test results on this patient's specimen?
5. One reason for Jason's failure to respond to ciprofloxacin may be due to infection with a fluoroquinolone-resistant *N. gonorrhoeae*. Susceptibility testing would be helpful to explore this possibility.

   The treatment and control of gonorrhea has been complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial agents (see the graph).
   How does antibiotic resistance emerge?
6. In an environment filled with antibiotics, bacteria that have mutations for antibiotic resistance will have a selective advantage and be the "fittest" to survive.
   How is antibiotic susceptibility determined?
7. *N. gonorrhoeae* must be grown in culture for disk-diffusion or broth dilution tests for antimicrobial susceptibility. The increasing use of nonculture methods for gonorrhea diagnosis such as PCR and EIA is a major challenge to monitoring antimicrobial resistance in *N. gonorrhoeae*.

Source: Data from CDC. *Sexually Transmitted Disease Surveillance 1998* and *2012*.



Antibiotic resistance in *N. gonorrhoeae*.

epithelial cells as the gonococcus. *C. trachomatis* is also responsible for the STI lymphogranuloma venereum (discussed on pages 760–761) and trachoma (see page 602). Of special importance is the fact that five times as many cases are reported in women as in men. In women, it is responsible for many cases of pelvic inflammatory disease (discussed on page 757), plus eye infections and pneumonia in infants born to infected mothers. Genital chlamydial infections are also associated with an increased risk of cervical cancer. It's uncertain whether chlamydial infection is an independent factor in this risk or whether it's associated with coinfections with human papillomavirus (pages 763–764).

Because the symptoms are often mild in men and because women are usually asymptomatic, many cases of NGU go untreated. Although complications are not common, they can be serious. Men may develop inflammation of the epididymis. In women, inflammation of the uterine tubes may cause scarring, leading to sterility. As many as 60% of such cases may be from chlamydial rather than gonococcal infection. It's estimated that about 50% of men and 70% of women are unaware of their chlamydial infection.

For diagnosis, culturing is the most reliable method, but this requires specialized cultivation methods, takes 24 to 72 hours, and is not always conveniently available. There are a number of new non–culture-based tests available. Several of them amplify and detect DNA or RNA sequences of *C. trachomatis*. These amplification tests can be done quickly and are very sensitive; their specificity is close to 100%. They are, however, relatively expensive and require a laboratory with specialized equipment.

Urine samples can be used, but the sensitivity is lower than with swabs. The most recent development in amplification testing is to use swab specimens (urethral or vaginal, as the case might be) collected by the patients themselves—which they tend to prefer.

In view of the serious complications often associated with infections by *C. trachomatis,* it's recommended that physicians routinely screen sexually active women 25 years of age and younger for infection. Screening is also recommended for other higher-risk groups, such as persons who are unmarried, had a prior risk of STIs, and have multiple sexual partners.

Bacteria other than *C. trachomatis* can also be implicated in NGU. Another cause of urethritis and infertility is *Ureaplasma urealyticum* (u′rē-ah-PLAZ-mah u′rē-ah-LIT-i-kum). This pathogen is a member of the mycoplasma (bacteria without a cell wall). Another mycoplasma, *Mycoplasma hominis* (mī-kō-PLAZ-mah HAH-mi-nis), commonly inhabits the normal vagina but can opportunistically cause uterine tube infection.

Both chlamydia and mycoplasma are sensitive to tetracycline-type antibiotics, such as doxycycline, or to macrolide-type antibiotics, such as azithromycin.

Pelvic Inflammatory Disease (PID)

Pelvic inflammatory disease (PID) is a collective term for any extensive bacterial infection of the female pelvic organs, particularly the uterus, cervix, uterine tubes, or ovaries. During their reproductive years, one in ten women suffers from PID, and one in four of these will have serious complications such as infertility or chronic pain.

Pelvic inflammatory disease is considered to be a *polymicrobial infection*—that is, a number of different pathogens might be the cause, including coinfections. The two most common microbes are *N. gonorrhoeae* and *C. trachomatis.* The onset of chlamydial PID is relatively more insidious, with fewer initial inflammatory symptoms than when caused by *N. gonorrhoeae.* However, the damage to the uterine tube may be greater with chlamydia, especially with repeated infections.

The bacteria may attach to sperm cells and be transported by them from the cervical region to the uterine tubes. Women who use barrier contraceptives, especially with spermicides, have a significantly lower rate of PID.

Infection of the uterine tubes, or **salpingitis,** is the most serious form of PID (**Figure 26.8**). Salpingitis can result in scarring that blocks the passage of ova from the ovary to the uterus, possibly causing sterility. One episode of salpingitis causes infertility in 10–15% of women; 50–75% become infertile after three or more such infections.

A blocked uterine tube may cause a fertilized ovum to be implanted in the tube rather than the uterus. This is called an *ectopic* (or *tubal*) *pregnancy,* and it is life-threatening because of the possibility of rupture of the tube and resulting hemorrhage. The reported cases of ectopic pregnancies have been increasing steadily, corresponding to the increasing occurrence of PID.

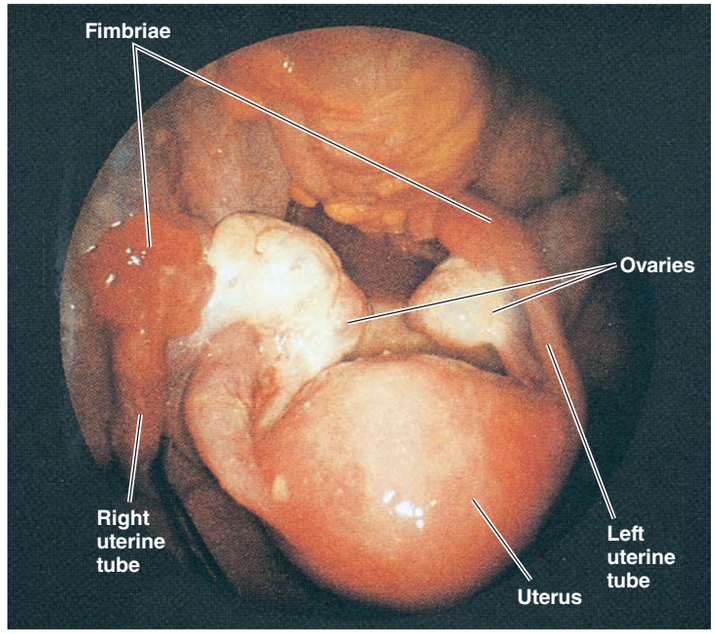


Figure 26.8 Salpingitis. This photograph, taken through a laparoscope (a specialized endoscope), shows an acutely inflamed right uterine tube and inflamed, swollen fimbriae and ovary, caused by salpingitis. The left tube is only mildly inflamed. (See Figure 26.2.) The use of a laparoscope is the most reliable diagnostic method for PID.

Q What is PID?

A diagnosis of PID depends strongly on signs and symptoms, in combination with laboratory indications of a gonorrheal or chlamydial infection of the cervix. The recommended treatment for PID is the simultaneous administration of doxycycline and cefoxitin (a cephalosporin). This combination is active against both the gonococcus and chlamydia. Such recommendations are constantly being reviewed.

Syphilis

The causative agent of **syphilis** is a gram-negative spirochete, *Treponema pallidum* (**Figure 26.9**). Thin and tightly coiled, *T. pallidum* stains poorly with the usual bacterial stains. (The bacterial name is derived from the Greek words for twisted thread and pale.) *T. pallidum* lacks the enzymes necessary to build many complex molecules; therefore, it relies on the host for many of the compounds necessary for life. The organism loses infectiveness outside the mammalian host within a short time. For research purposes they are usually propagated in rabbits, but they grow slowly, with a generation time of 30 hours or more. They can be grown in cell culture, at low oxygen concentrations, but only for a few generations.

T. pallidum has no obvious virulence factors such as toxins, but it produces several lipoproteins that induce an inflammatory immune response. This is what apparently causes the tissue destruction of the disease. Almost immediately on infection,

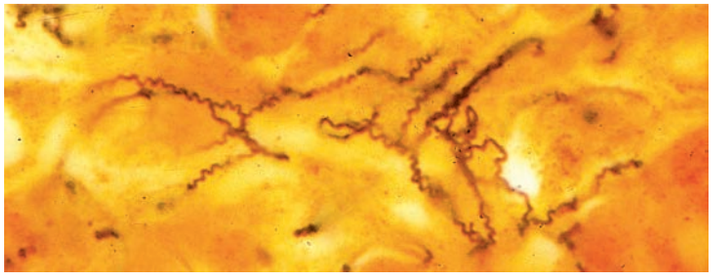


Figure 26.9 ***Treponema pallidum,* the cause of syphilis.** The microbes are made more visible in this brightfield micrograph by the use of a special silver stain.

Q A diagnostic method for syphilis is the darkfield microscope. Why not use a brightfield microscope?

the organisms rapidly enter the bloodstream and invade deeper tissues, easily crossing the junctions between cells. They have a corkscrew-like motility that allows them to swim readily in gel-like tissue fluids.

The earliest reports of syphilis date back to the end of the fifteenth century in Europe, when the return of Columbus from the New World gave rise to a hypothesis that syphilis was introduced to Europe by his men. One English description of the "Morbus Gallicus" (French disease) seems to clearly describe syphilis as early as 1547 and ascribes its transmission in these terms: ". . . It is taken when one pocky person doth synne in lechery one with another."

Separate strains of *T. pallidum* (subspecies *T.p. pertenue*) are responsible for certain tropically endemic skin diseases such as **yaws.** These cause skin lesions but are not sexually transmitted. However, there is evidence of a probable historical association with syphilis. Current research based on genetic analysis of *Treponema* spp. indicates that a pathogen of yaws found in South America adjacent to the Caribbean mutated into a sexually transmitted disease on contact with European explorers.

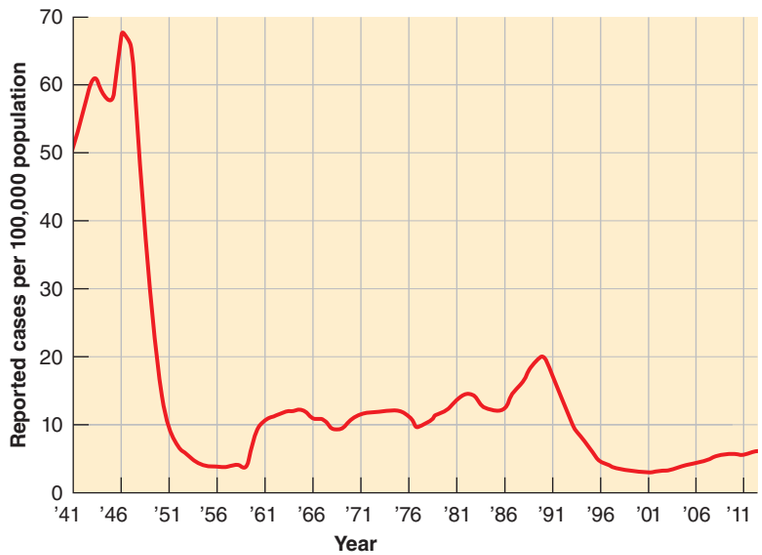
The number of new syphilis cases in the United States has remained fairly stable (**Figure 26.10**) compared with gonorrhea (see Figure 26.5). The relative stability in the incidence of syphilis is remarkable because the epidemiology of the two diseases is quite similar, and concurrent infections are not uncommon. A factor is that syphilis results in a significant, if imperfect, immunity—compared to no conferred immunity from gonorrhea.

Many states discontinued the requirements for premarital syphilis tests because so few cases were detected. At present, the population most at risk is economically disadvantaged inner city residents, especially drug-using prostitutes of both sexes. It is relatively rare in affluent societies.

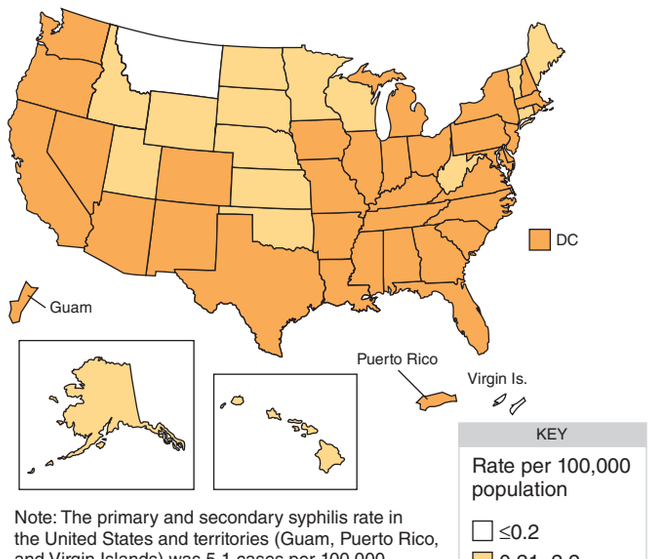
Syphilis is transmitted by sexual contact of all kinds via syphilitic infections of the genitals or other body parts. The incubation period averages 3 weeks but can range from 2 weeks to several months. The disease progresses through several recognized stages.

Primary Stage Syphilis

In the *primary stage* of the disease, the initial sign is a small, hard-based **chancre,** or sore, which appears at the site of



(a) Incidence of syphilis in the United States, 1941–2013



Note: The primary and secondary syphilis rate in the United States and territories (Guam, Puerto Rico, and Virgin Islands) was 5.1 cases per 100,000 population.

(b) Geographical distribution of cases in 2012

Figure 26.10 The U.S. incidence and distribution of primary and secondary syphilis.

Source: CDC, 2014.

Q How is syphilis diagnosed?

infection 10 to 90 days following exposure—on average, about 3 weeks (**Figure 26.11a**). The chancre is painless, and an exudate of serum forms in the center. This fluid is highly infectious, and examination with a darkfield microscope shows many spirochetes. In a couple of weeks, this lesion disappears. None of these symptoms causes any distress. In fact, many women are entirely unaware of the chancre, which is often on the cervix. In men, the chancre sometimes forms in the urethra and isn't visible. During this stage, bacteria enter the bloodstream and lymphatic system, which distribute them widely in the body.

Secondary Stage Syphilis

Several weeks after the primary stage (the exact length of time varies and may overlap), the disease enters the *secondary stage,* characterized mainly by skin rashes of varying appearance. The rash is widely distributed on the skin and mucous membranes and is especially visible on the palms and on the soles (Figure 26.11b). The damage done to tissues at this stage and the later tertiary stage is caused by an inflammatory response to circulating immune complexes that lodge at various body sites. Other symptoms often observed are the loss of patches of hair, malaise, and mild fever. A few people may exhibit neurological symptoms.

At this stage, the lesions of the rash contain many spirochetes and are very infectious. Transmission from sexual contact occurs during the primary and secondary stages. Dentists and other health care workers coming into contact with fluid from these lesions can become infected by the spirochete entering through minute breaks in the skin. Such nonsexual transmission is possible, but the microbes don't survive long on environmental surfaces and are very unlikely to be transmitted via such objects as toilet seats. Secondary syphilis is a subtle disease; at least half of the patients diagnosed with this stage can recall no lesions at all. Symptoms usually resolve within 3 months.

Latent Period

The symptoms of secondary syphilis will go away with or without treatment, and the disease enters a *latent period.* During this period, there are no symptoms. After 2 to 4 years of latency, the disease is not normally infectious, except for transmission from mother to fetus. The majority of cases don't progress beyond the latent stage, even without treatment.

Tertiary Stage Syphilis

Because the symptoms of primary and secondary syphilis aren't disabling, people may enter the latent period without having received medical attention. In up to 25% of untreated cases, the disease reappears in a *tertiary stage.* This stage occurs only after an interval of many years from the onset of the latent phase.

T. pallidum has an outer layer of lipids that stimulates little effective immune response, especially from cell-destroying complement reactions. It has been described as a "Teflon pathogen." Nonetheless, most of the symptoms of tertiary syphilis are probably due to the body's immune reactions (of a cell-mediated nature) to surviving spirochetes.



(a) Chancre of primary stage on a male in genital area



(b) Lesions of secondary syphilis rash on a forearm; any surface of the body may be afflicted with such lesions.



(c) Gummas of tertiary stage on the back of a forearm; gummas such as these are rarely seen today in the era of antibiotics.

Figure 26.11 Characteristic lesions associated with various stages of syphilis.

Q How are the primary, secondary, and tertiary stages of syphilis distinguished?

Tertiary, or late-stage, syphilis can be classified generally by affected tissues or type of lesion. *Gummatous syphilis* is characterized by **gummas,** which are a form of progressive inflammation

that appear as rubbery masses of tissue (Figure 26.11c) in various organs (most commonly the skin, mucous membranes, and bones) after about 15 years. There they cause local destruction of these tissues but usually not incapacitation or death.

Cardiovascular syphilis results most seriously in a weakening of the aorta. In preantibiotic days, it was one of the more common symptoms of syphilis; it is now rare.

Neurosyphilis occurs in up to 10% of patients if the disease is untreated. As parts of the central nervous system are affected, the result can be widely varying signs and symptoms. The patient can suffer from personality changes and other signs of dementia (*paresis*), seizures, loss of coordination of voluntary movement (*tabes dorsalis*), partial paralysis, loss of ability to use or comprehend speech, loss of sight or hearing, or loss of bowel and bladder control. Few, if any, pathogens are found in the lesions of the tertiary stage, and they are not considered very infectious. Today, it is rare for cases of syphilis to be allowed to progress to this stage.

Congenital Syphilis

One of the most distressing and dangerous forms of syphilis, called **congenital syphilis,** is transmitted across the placenta to the unborn fetus. Damage to mental development and other neurological symptoms are among the more serious consequences. This type of infection is most common when pregnancy occurs during the latent period of the disease. A pregnancy during the primary or secondary stage is likely to produce a stillbirth. Treating the mother with antibiotics during the first two trimesters (6 months) will usually prevent congenital transmission.

Diagnosis of Syphilis

Diagnosis of syphilis is complex because each stage of the disease has unique requirements. Tests fall into three general groups: visual microscopic inspection, nontreponemal serological tests, and treponemal serological tests. For preliminary screening, laboratories use either nontreponemal serological tests or microscopic examination of exudates from lesions when these are present. If a screening test is positive, the results are confirmed by treponemal serological tests.

Microscopic tests are important for screening for primary syphilis because serological tests for this stage are not reliable; antibodies take 1 to 4 weeks to form. The spirochetes can be detected in exudates of lesions by microscopic examination with a darkfield microscope (see Figure 3.4b, page 57). A darkfield microscope is necessary because the bacteria stain poorly and are only about 0.2 µm in diameter, near the lower limit of resolution for a brightfield microscope. Similarly, a **direct fluorescent-antibody test (DFA-TP)** using monoclonal antibodies (see Figure 18.11a, page 508) will both show and identify the spirochete. Figure 26.9 shows *T. pallidum* under brightfield illumination made possible by a special silver-impregnated stain.

At the secondary stage, when the spirochete has invaded almost all body organs, serological tests are reactive. *Nontreponemal serological tests* are so called because they are nonspecific; they detect *reagin-type antibodies,* not the antibodies produced against the spirochete itself. Generally, these tests are used for screening. Reagin-type antibodies are apparently a response to lipid materials the body forms as an indirect reaction to infection by the spirochete. The antigen used in such tests is thus not the syphilis spirochete but an extract of beef heart (cardiolipin) that seems to contain lipids similar to those that stimulated the reagin-type antibody production. These tests will detect only about 70–80% of primary syphilis cases, but they will detect 99% of secondary syphilis cases. An example of nontreponemal tests is the slide agglutination **VDRL test** (for Venereal Disease Research Laboratory). Also used are modifications of the **rapid plasma reagin (RPR) test,** which is similar. The newest nontreponemal test is an ELISA test that uses the VDRL antigen.

There are also *treponemal-type serological tests* that react directly with the spirochete. Certain **enzyme immunoassay (EIA)** treponemal tests can be done in many laboratories and offer high-throughput screening. There are also simple **rapid diagnostic tests (RDTs)** of this type that can be done from a finger-prick blood sample in a physician's office. Neither of these groups of tests will distinguish a prior from an active infection; confirmatory tests, which usually must be done at a central reference laboratory, are required.

Only treponemal-type tests are used for confirmatory testing. An example is the **fluorescent treponemal antibody absorption test,** or **FTA-ABS test,** an indirect fluorescent-antibody test (see Figure 18.11b, page 508). Treponemal tests are not used for screening because about 1% of the results will be false positives, but a positive test with both treponemal and nontreponemal types is highly specific.

Treatment of Syphilis

Benzathine penicillin, a long-acting formulation that remains effective in the body for about 2 weeks, is the usual antibiotic treatment of syphilis. The serum concentrations achieved by this formulation are low, but the spirochete has remained very sensitive to this antibiotic.

For penicillin-sensitive people, several other antibiotics, such as azithromycin, doxycycline, and tetracycline, have also proven effective.

Lymphogranuloma Venereum (LGV)

Several STIs that are uncommon in the United States occur frequently in the tropical areas of the world. For example, *Chlamydia trachomatis,* the cause of the eye infection trachoma and a major cause of NGU, is also responsible for **lymphogranuloma venereum (LGV),** a disease found in tropical and near-tropical regions. It is apparently caused by serovars of *C. trachomatis* that are invasive and tend to infect lymphoid tissue. In the United States, there are usually 200 to 400 cases each year, mostly in homosexual men, many of whom are also HIV-positive.

The microorganisms invade the lymphatic system, and the regional lymph nodes become enlarged and tender. Suppuration

(a discharge of pus) may also occur. Inflammation of the lymph nodes results in scarring, which occasionally obstructs the lymph vessels. This blockage sometimes leads to massive enlargement of the external genitals in men. In women, involvement of the lymph nodes in the rectal region leads to narrowing of the rectum. These conditions may eventually require surgery.

For diagnosis, blood tests for antibodies to the serovars of *C. trachomatis* causing the disease are the most satisfactory. The isolated organisms can also be grown in cell culture or in embryonated eggs, but not all laboratories have the facilities for this. The drug of choice for treatment is doxycycline.

Chancroid (Soft Chancre)

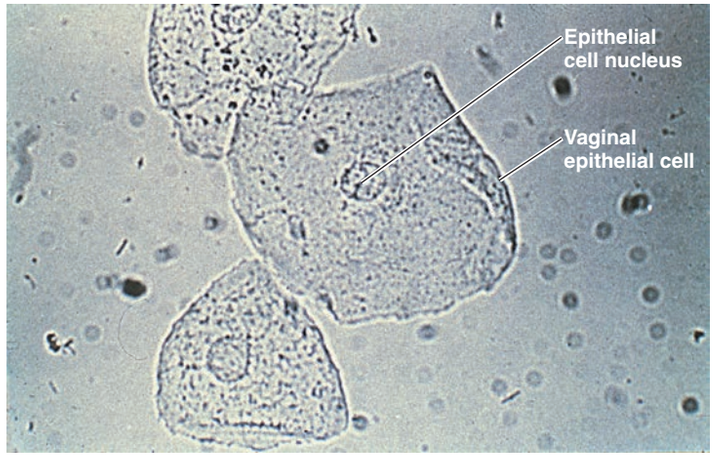
The STI known as **chancroid (soft chancre)** occurs most frequently in tropical areas, where it is seen more often than syphilis. The number of reported cases in the United States has been declining from a peak of 5000 cases in 1988. Like syphilis, its incidence is strongly associated with drug use. Because chancroid is so seldom seen by some physicians and is difficult to diagnose, it's probably underreported. It's very common in Africa, Asia, and Latin America.

In chancroid, a swollen, painful ulcer that forms on the genitals involves an infection of the adjacent lymph nodes. Infected lymph nodes in the groin area sometimes even break through and discharge pus to the surface. Such lesions are an important factor in the sexual transmission of HIV, especially in Africa. Lesions might also occur on such diverse areas as the tongue and lips. The causative agent is *Haemophilus ducreyi* (hē-MAH-fil-us doo-KRĀ-ē), a small gram-negative rod that can be isolated from exudates of lesions. Symptoms and the culture of these bacteria are the primary means of diagnosis. The recommended antibiotics include single doses of azithromycin or ceftriaxone.

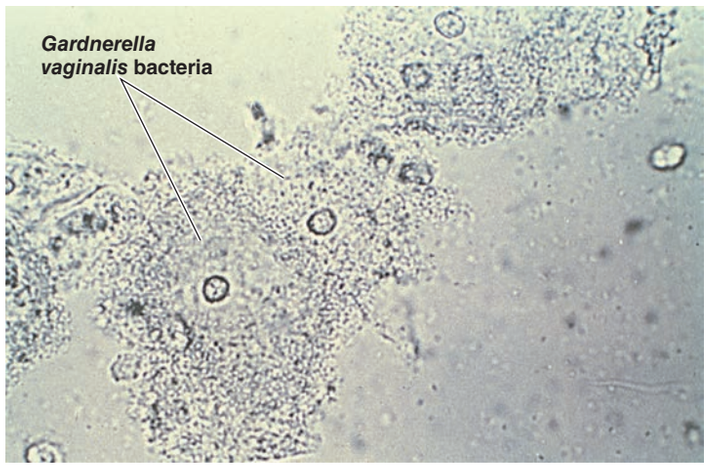
Bacterial Vaginosis

Inflammation of the vagina due to infection, or **vaginitis,** is most commonly caused by one of several organisms: mainly the fungus *Candida albicans* (KAN-dē-dah AL-bi-kanz), the protozoan *Trichomonas vaginalis* (TRIK-ō-mō-nas VA-jin-al-is), or the bacterium *Gardnerella vaginalis,* a small, pleomorphic gram-variable rod (see Diseases in Focus 26.2 on page 764). Most of these cases are attributed to the presence of *G. vaginalis* and are termed **bacterial vaginosis.** (Because there is no sign of inflammation, the term *vaginosis* is preferred to *vaginitis*).

The condition is something of an ecological mystery. It's believed that bacterial vaginosis is precipitated by some event that decreases the number of *Lactobacillus* vaginal bacteria that normally produce hydrogen peroxide. This competitive change allows bacteria, especially *G. vaginalis,* to proliferate, producing amines that contribute to a further rise in pH. These various bacteria, most of which are commonly found in the vaginas of asymptomatic women, are assumed to be metabolically interdependent. This situation does not lend itself to the application of Koch's postulates to determine a specific cause. There is no corresponding disease condition in men, but *G. vaginalis* is often present in their urethras. Therefore, the condition may be sexually transmitted, but it also occurs occasionally in women who have never been sexually active.



(a) Normal vaginal epithelial cell LM 12.5 μm



(b) Clue cell LM 12 μm

Figure 26.12 Clue cells. *Gardnerella* bacteria coat the surface of vaginal epithelial cells.

Q What symptoms would cause you to look for clue cells?

Bacterial vaginosis is characterized by a vaginal pH above 4.5 and a copious, frothy vaginal discharge. When tested with a potassium hydroxide solution, these vaginal secretions emit a fishy odor from presence of the amines produced by *G. vaginalis.* Diagnosis is based on the vaginal pH, fishy odor (the *whiff test*), and microscopic observation of *clue cells* in the discharge. These clue cells are sloughed-off vaginal epithelial cells covered with a biofilm of bacteria, mostly *G. vaginalis* (**Figure 26.12**). The disease has been considered more of a nuisance than a serious infection, but it's now seen as a factor in many premature births and low birth-weight infants.

Clinical Case Resolved

IgG antibodies against *L. interrogans* can persist for years, and their presence may only indicate a previous exposure. The rise in titer on the second test indicates a current infection. Maricel is treated with doxycycline for leptospirosis and is soon able to resume training for her next kayaking event.

Occupational exposure most likely accounts for 30–50% of human cases of leptospirosis. The main occupational groups at risk include farm workers, veterinarians, pet shop owners, plumbers and sewer workers, meat handlers and slaughterhouse workers, and military troops. However, since 1970 leptospirosis has been increasingly associated with recreational activities. Prolonged water exposure from swimming or kayaking in freshwater lakes or streams, for example, has been associated with *L. interrogans* infection.

747 751 755 762

Treatment is primarily by metronidazole, a drug that eradicates the anaerobes essential to continuation of the disease but allows the normal lactobacilli to repopulate the vagina. Treatments designed to restore the normal population of lactobacilli, such as application of acetic acid gels and even yogurt, have not been shown conclusively to be effective.

CHECK YOUR UNDERSTANDING

Why is the disease condition of the female reproductive system, principally featuring growth of *Gardnerella vaginalis,* termed *vaginosis* rather than *vaginitis*? **26-6**

Viral Diseases of the Reproductive Systems

LEARNING OBJECTIVE

26-7 Discuss the epidemiology of genital herpes and genital warts.

Viral diseases of the reproductive system are difficult to treat, and so they represent an increasing health problem.

Genital Herpes

A much publicized STI is **genital herpes,** usually caused by *herpes simplex virus type 2* (HSV-2). (The herpes simplex virus occurs as either type 1 or type 2.) Herpes simplex virus type 1 (HSV-1) is primarily responsible for cold sores or fever blisters (see page 593), but it can also cause genital herpes. The official names are human herpesvirus 1 and 2.

In the United States, one in four persons over the age of 30 is infected with HSV-2—most are unaware they are infected (**Figure 26.13**). There has been a marked increase in genital HSV-1 infections, which is usually acquired by oral–genital contact, and this now constitutes about half of cases of genital herpes in this country.

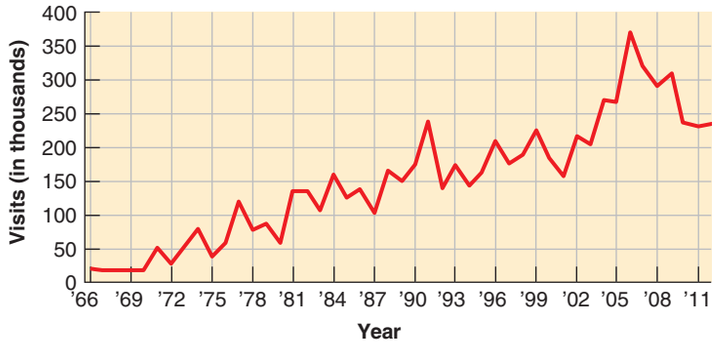


Figure 26.13 Genital herpes: initial visits to physicians' offices, United States, 1966 to 2012.

Source: CDC, 2013.

What are possible causes for changes in the incidence of a disease, such as shown on this graph?

Genital herpes lesions appear after an incubation period of up to 1 week and cause a burning sensation. After this, vesicles appear (**Figure 26.14**). In both men and women, urination can be painful, and walking is quite uncomfortable; the patient is even irritated by clothing. Usually, the vesicles heal in a couple of weeks.

The vesicles contain infectious fluid, but many times the disease is transmitted when no lesions or symptoms are apparent. Semen may contain the virus. Condoms may not provide protection because in women the vesicles are usually on the external genitals (seldom on the cervix or within the vagina), and in men the vesicles may be on the base of the penis.

One of the most distressing characteristics of genital herpes is the possibility of recurrences. There is an element of truth in the medical adage that, unlike love, herpes is forever. As in other herpes infections, such as cold sores or chickenpox-shingles, the virus

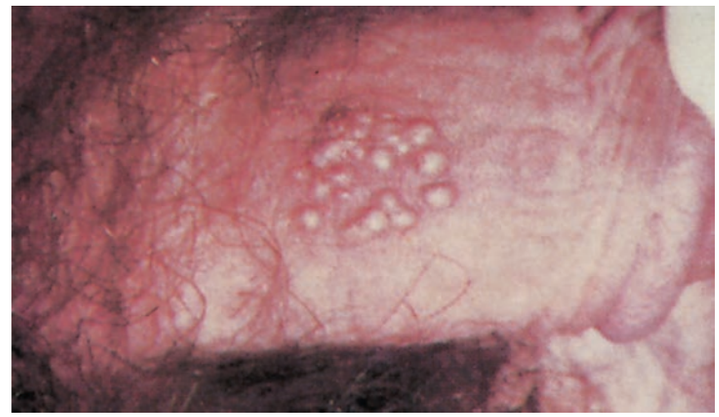


Figure 26.14 Vesicles of genital herpes on a penis.

What microbe causes genital herpes?

enters a lifelong latent state in nerve cells. Some people have several recurrences a year; for others, recurrence is rare. Men are more likely to experience recurrences than women. Reactivation appears to be triggered by several factors, including menstruation, emotional stress or illness (especially if accompanied by fever, a factor that is also involved in the appearance of cold sores), and perhaps just scratching the affected area. About 90% of patients with HSV-2 and about 50% of those with HSV-1 will have recurrences. Recurrence rates decrease over time, regardless of treatment.

Diagnosis of genital herpes can be done by culture of the virus taken from a vesicle; however, PCR testing of such samples has proven more sensitive and is potentially faster. If there are no lesions to be sampled, serological testing can identify HSV infections or confirm clinical diagnosis by symptoms.

There is no cure for genital herpes, although research on its prevention and treatment is intensive. Discussions of chemotherapy use terms such as *suppression* or *management* rather than *cure*. Currently, the antiviral drugs acyclovir, famciclovir, and valacyclovir are recommended for treatment. They are fairly effective in alleviating the symptoms of a primary outbreak; there is some relief of pain and slightly faster healing. Taken over several months they lower the chances of recurrence during that time.

Neonatal Herpes

Neonatal herpes is a serious consideration for women of childbearing age. The virus can cross the placental barrier and affect the fetus, causing spontaneous abortion or serious fetal damage. If untreated, a survival rate of only about 40% can be expected, and even treated survivors will have considerable disability. Herpes infection of the newborn is most likely to have serious consequences when the mother acquires the initial herpes infection during the pregnancy. If tests show a pregnant woman has no antibodies against herpes viruses, she requires special counseling to avoid an initial infection. Exposure to recurrent or asymptomatic herpes is much less likely to damage the fetus, most likely because of protective maternal antibodies.

Most infections of the newborn occur from exposure to HSV during delivery. HSV-2 infections are likely to be more serious than HSV-1 infections. If genital sores that might be caused by herpes infection are present at the time of delivery, a sample can be taken and isolates tested to determine whether they are HSV-1 or HSV-2. If the culture is negative but a herpes infection is still suspected, a PCR test for viral DNA can be done. It is rather common for pregnant women to be shedding HSV-2 even though they show no evidence of an infection. Even so, fewer than 1% of newborns develop neonatal herpes, which is also probably because of protective antibodies.

Some newborns have infections that are confined to the skin, mucous membranes, and eyes. With proper treatment, the outcome of these cases is usually good. However, about 30% of the cases are associated with damage to the central nervous system that may include developmental delays, blindness, hearing loss, or epilepsy. Disseminated viral infections can result in death of the newborn.

Culture and identification of the virus take a few days, but fluorescent antibody tests can quickly detect viral protein, or PCR tests can detect the presence of viral DNA. Treatment usually involves intravenous administration of acyvlovir. No vaccine is currently available.

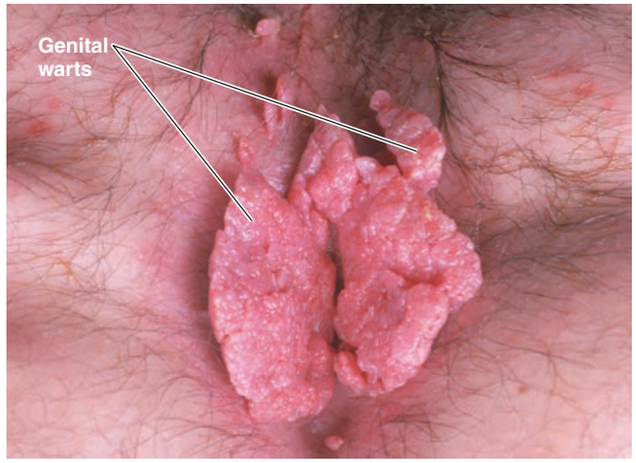


Figure 26.15 Genital warts on a vulva.

Q What is the relationship between genital warts and cervical cancer?

Genital Warts

Warts are an infectious disease caused by viruses known as papillomaviruses. (See Chapter 21 for more-familiar, skin-associated, warts.) Many papillomaviruses have a predilection for growth not on the skin, but on the mucous membranes that line organs such as the respiratory tract, mouth, anus, and genitalia. Such **genital warts** (or condyloma acuminata) are usually transmitted sexually and are an increasing problem. Nearly 1 million new cases are estimated to occur in the United States each year; recent testing showed that more than one-fourth of women in the United States aged 14 to 59 years were infected. Worldwide, genital warts may well be the most common STI.

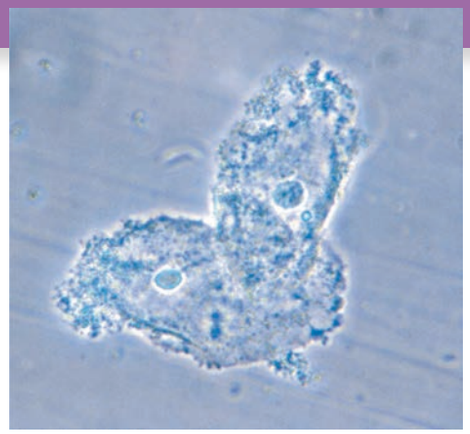
There are more than 60 types of human papillomaviruses (HPV), and certain serotypes tend to be linked with certain forms of genital warts. For example, some genital warts are extremely large, resembling a cauliflower with multiple fingerlike projections, whereas others are relatively smooth or flat (**Figure 26.15**).

Penile lesions are often flat and quite inapparent, an important factor in male to female transmission. The incubation period is usually a matter of a few weeks or months. Visible genital warts are most often caused by serotypes 6 and 11. These serotypes rarely cause cancer, which is the most serious concern with these infections. The types most likely to cause cancer are types 16 and 18, but these have a relatively low prevalence. Even so, cervical cancer caused by HPV kills at least 4000 women

DISEASES IN FOCUS 26.2

Characteristics of the Most Common Types of Vaginitis and Vaginosis

Vaginitis, or inflammation of the vagina, often accompanies vaginal infections. Vaginitis may be caused by microbial infections. The cause of vaginitis cannot be determined on the basis of symptoms or physical examination alone. Usually, diagnosis involves examining a specimen of vaginal fluid under a microscope (see the photo). Use the table below to identify the infection caused by the organism in the figure. For the solution, go to MasteringMicrobiology.



Epithelial cells covered with rod-shaped bacteria from a vaginal swab.

Disease	Pathogen	Symptoms				Diagnosis	Treatment
		Odor, Color, and Consistency of Discharge	*Amount of Discharge*	*Appearance of Vaginal Mucosa*	*pH (normal pH is 3.8–4.2)*		
Candidiasis	Fungus, *Candida albicans*	Yeasty or none, white, curdy	Varies	Dry, red	<4	Microscopic exam	Clotrimazole; fluconazole
Bacterial Vaginosis	Bacterium, *Gardnerella vaginalis*	Fishy; gray-white, thin, frothy	Copious	Pink	>4.5	Presence of clue cells	Metronidazole
Trichomoniasis	Protozoan, *Trichomonas vaginalis*	Foul, greenish-yellow; frothy	Copious	Tender, red	5–6	Microscopic exam; DNA probes; monoclonal antibody	Metronidazole

annually in the United States. Oral, anal, and penile cancers are also attributed to HPV infections.

Two vaccines (Gardasil and Cervarix) have been licensed that are effective against the HPV types most likely to cause cancer. The vaccines are recommended for adolescents aged 11 through 12 years, and are even required in some areas. The immune response to the vaccines is much more effective than that resulting from a natural infection, which is relatively weak.

Warts can be treated but not cured (see the discussion on page 590), but approximately 90% of cases clear spontaneously within 2 years. The available methods used for warts, such as surgery or cryotherapy, are not as effective against genital warts. Two patient-applied gels, podofilox and imiquimod, are often useful treatments. Imiquimod (Aldara) stimulates the body to produce interferon (page 460), which appears to account for its antiviral activity.

AIDS

AIDS, or HIV infection, is a viral disease that is frequently transmitted by sexual contact. However, its pathogenicity is based on damage to the immune system, so it is discussed on pages 534–544. It's important to remember that the lesions resulting from many of the diseases of bacterial and viral origin facilitate the transmission of HIV.

CHECK YOUR UNDERSTANDING

Both genital herpes and genital warts are caused by viruses; which one is the greater danger to a pregnancy? **26-7**

Fungal Disease of the Reproductive Systems

LEARNING OBJECTIVE

26-8 Discuss the epidemiology of candidiasis.

The fungal disease described here is the well-known *yeast infection* for which nonprescription treatments are advertised.

Candidiasis

Vaginal infections by yeastlike fungi of the genus *Candida* are responsible for millions of physician office visits every year. By the time they reach the age of 25, an estimated half of college women will have had at least one physician-diagnosed episode. Nonprescription antifungal therapies to treat these infections are among the best-selling over-the-counter products in the United States. *Candida albicans* is the most common species, causing 85–90% of cases. Infections by other species, such as *C. glabrata,* are more likely to be resistant to antifungals and to be chronic or recurrent.

C. albicans often grows on mucous membranes of the mouth, intestinal tract, and genitourinary tract (see Diseases in Focus 26.2; see also Figure 21.17, page 597). Infections are usually a result of opportunistic overgrowth when the competing microbiota are suppressed by antibiotics or other factors. *C. albicans* is the cause of **oral candidiasis,** or thrush (see Chapter 21). It's also responsible for occasional cases of NGU in men and for **vulvovaginal candidiasis,** which is the most common cause of vaginitis. About 75% of all women experience at least one episode.

The lesions of vulvovaginal candidiasis resemble those of thrush but produce more irritation: severe itching; a thick, yellow, cheesy discharge; and yeasty or no odor. *C. albicans,* the *Candida* species responsible for most cases, is an opportunistic pathogen. Predisposing conditions include the use of oral contraceptives and pregnancy, which cause an increase of glycogen in the vagina (see the discussion of the normal vaginal microbiota on page 748). Hormones are probably a factor; candidiasis is much less common in girls before puberty or in women after menopause. Yeast infections are a frequent symptom in women suffering from uncontrolled diabetes. Thus, diabetes and antibiotic therapy are predisposing factors to *C. albicans* vaginitis.

A yeast infection is diagnosed by microscopic identification of the fungus in scrapings of lesions and by isolation of the fungus in culture. Treatment usually consists of topical application of nonprescription antifungal drugs such as clotrimazole and miconazole. An alternative treatment is a single dose of oral fluconazole or other azole-type antifungal.

CHECK YOUR UNDERSTANDING

- What changes in the vaginal bacterial microbiota tend also to favor the growth of the yeast *Candida albicans*? **26-8**

Protozoan Disease of the Reproductive Systems

LEARNING OBJECTIVES

26-9 Discuss the epidemiology of trichomoniasis.

26-10 List reproductive system diseases that can cause congenital and neonatal infections, and explain how these infections can be prevented.

The only STI caused by a protozoan affects mostly young, sexually active women. It may be the most common STI—nearly 8 million cases per year are reported in the United States—but it isn't widely known. Its prevalence in certain STI clinics is 25% or higher.



Figure 26.16 ***Trichomonas vaginalis*** **adhering to the surface of an epithelial cell in a cell culture preparation.** The flagella are clearly visible.

Source: D. Petrin et al., "Clinical and Microbiological Aspects of *Trichomonas vaginalis*." *ASM Clinical Microbiology Reviews* 11 (1998): 300–317.

Q Are there any harmful effects from infection by this protozoan?

Trichomoniasis

The anaerobic protozoan *Trichomonas vaginalis* is frequently a normal inhabitant of the vagina in women and of the urethra in many men (**Figure 26.16**). It's usually sexually transmitted. If the normal acidity of the vagina is disturbed, the protozoan may overgrow the normal microbial population of the genital mucosa and cause **trichomoniasis.** (Men rarely have any symptoms resulting from the presence of the protozoan.) The infection is often accompanied by a coinfection with gonorrhea. In response to the protozoan infection, the body accumulates leukocytes at the infection site. The resulting discharge is profuse, greenish yellow, and characterized by a foul odor. This discharge is accompanied by irritation and itching. Up to half the cases, however, are asymptomatic.

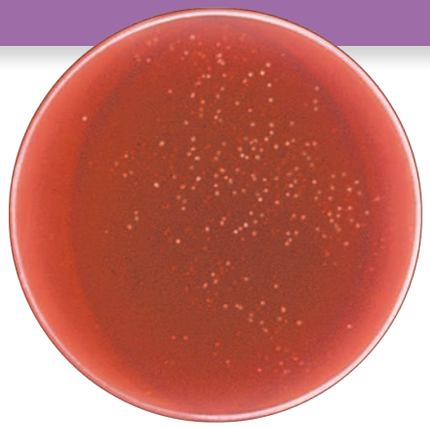
The incidence of trichomoniasis is higher than that of gonorrhea or chlamydia, but it is considered relatively benign and is not a reportable disease. It's known, however, to cause preterm delivery and associated problems, such as low birth weight.

Diagnosis is usually made by microscopic examination and identification of the organisms in the discharge. They can also

DISEASES IN FOCUS 26.3

Microbial Diseases of the Reproductive Systems

A 26-year-old woman has abdominal pain, painful urination, and fever. Cultures grown in a high-CO_2 environment reveal gram-negative diplococci. Use the table below to identify infections that could cause these symptoms. For the solution, go to MasteringMicrobiology.



Gram-negative diplococci on Thayer-Martin agar, which is a blood-containing medium with antibiotics to encourage the growth of this pathogen and inhibit the growth of unwanted microbes.

Disease	Pathogen	Symptoms	Treatment
BACTERIAL DISEASES			
Gonorrhea	*Neisseria gonorrhoeae*	Men: painful urination and discharge of pus. Women: few symptoms but possible complications, such as PID.	Cephalosporins
Nongonococcal Urethritis (NGU)	*Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum*	Painful urination and watery discharge. In women, possible complications, such as PID.	Doxycycline, azithromycin
Pelvic Inflammatory Disease (PID)	*N. gonorrhoeae, C. trachomatis*	Chronic abdominal pain; possible infertility	Doxycycline and cefoxitin
Syphilis	*Treponema pallidum*	Initial sore at site of infection, later skin rashes and mild fever; final stages may be severe lesions, damage to cardiovascular and nervous systems.	Benzathine penicillin
Lymphogranuloma Venereum (LGV)	*C. trachomatis*	Swelling in lymph nodes in groin	Doxycycline
Chancroid (Soft Chancre)	*Haemophilus ducreyi*	Painful ulcers of genitals; swollen lymph nodes in groin	Erythromycin; ceftriaxone
Bacterial Vaginosis	See Diseases in Focus 26.2 page 764		
VIRAL DISEASES			
Genital Herpes	Herpes simplex virus type 2; HSV type 1	Painful vesicles in genital area	Acyclovir
Genital Warts	Human papillomaviruses	Warts in genital area	Podofilox; imiquimod; preventive vaccine
AIDS	See Chapter 19, pp. 534–544		
FUNGAL DISEASE			
Candidiasis	See Diseases in Focus 26.2, page 764		
PROTOZOAN DISEASE			
Trichomoniasis	See Diseases in Focus 26.2, page 764		

be isolated and grown on laboratory media. The pathogen can be found in semen or urine of male carriers. New rapid tests making use of DNA probes and monoclonal antibodies are now available. Treatment is by oral metronidazole, administered to both sex partners, which readily clears the infection. The major microbial diseases of the urinary and reproductive systems are summarized in Diseases in Focus 26.3.

The TORCH Panel of Tests

We have seen in this and previous chapters that a number of diseases can cause birth defects in newborns when they infect a pregnant woman. TORCH is an acronym for a panel of tests that screens for antibodies to these infections in pregnant women. Confirmation may require additional testing. The panel is made up of the following: **T**oxoplasmosis; **O**ther (such as syphilis, hepatitis B, enterovirus, Epstein-Barr virus, varicella-zoster virus); **R**ubella; **C**ytomegalovirus; **H**erpes simplex virus.

CHECK YOUR UNDERSTANDING

- What are the symptoms of the presence of *Trichomonas vaginalis* in the male reproductive system? **26-9**
- What is the intent of the TORCH panel of tests? **26-10**

Study Outline

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Introduction (p. 746)

1. The urinary system regulates the chemical composition and volume of the blood and excretes nitrogenous waste and water.
2. The reproductive system produces gametes for reproduction and, in the female, supports the growing embryo.
3. Microbial diseases of these systems can result from infection from an outside source or from opportunistic infection by members of the normal microbiota.

Structure and Function of the Urinary System (p. 747)

1. Urine is transported from the kidneys through ureters to the urinary bladder and is eliminated through the urethra.
2. Valves prevent urine from flowing back to the urinary bladder and kidneys.
3. The flushing action of urine and normal urine itself have some antimicrobial value.

Structure and Function of the Reproductive Systems (pp. 747–748)

1. The female reproductive system consists of two ovaries, two uterine tubes, the uterus, the cervix, the vagina, and the external genitals.
2. The male reproductive system consists of two testes, ducts, accessory glands, and the penis; seminal fluid leaves the male body through the urethra.

Normal Microbiota of the Urinary and Reproductive Systems (p. 748)

1. The urinary bladder and upper urinary tract are sterile under normal conditions.
2. Lactobacilli dominate the vaginal microbiota during the reproductive years.
3. The male urethra is normally sterile.

Diseases of the Urinary System (pp. 749–751)

Bacterial Diseases of the Urinary System (pp. 749–751)

1. Urethritis, cystitis, and ureteritis are inflammations of tissues of the lower urinary tract.
2. Pyelonephritis can result from lower urinary tract infections or from systemic bacterial infections.
3. Opportunistic gram-negative bacteria from the intestines often cause urinary tract infections.
4. Nosocomial infections following catheterization occur in the urinary system. *E. coli* causes more than half of these infections.
5. Treatment of urinary tract infections depends on isolation and antibiotic sensitivity testing of the causative agents.

Cystitis (p. 749)

6. Inflammation of the urinary bladder, or cystitis, is common in females.
7. Microorganisms at the opening of the urethra and along the length of the urethra, careless personal hygiene, and sexual intercourse contribute to the high incidence of cystitis in females.
8. The most common etiologies are *E. coli* and *Staphylococcus saprophyticus*.

Pyelonephritis (p. 749)

9. Inflammation of the kidneys, or pyelonephritis, is usually a complication of lower urinary tract infections.
10. About 75% of pyelonephritis cases are caused by *E. coli*.

Leptospirosis (pp. 749–751)

11. The spirochete *Leptospira interrogans* is the cause of leptospirosis.
12. The disease is transmitted to humans by urine-contaminated water.
13. Leptospirosis is characterized by chills, fever, headache, and muscle aches.

Diseases of the Reproductive Systems (pp. 751–762)

Bacterial Diseases of the Reproductive Systems (pp. 751–762)

1. Most diseases of the reproductive system are sexually transmitted diseases (STDs), now called sexually transmitted infections (STIs).
2. Most STIs can be prevented by the use of condoms and are treated with antibiotics.

Gonorrhea (pp. 751–755)

3. *Neisseria gonorrhoeae* causes gonorrhea.
4. Gonorrhea is a common reportable communicable disease in the United States.
5. *N. gonorrhoeae* attaches to mucosal cells of the oral-pharyngeal area, genitals, eyes, and rectum by means of fimbriae.
6. Symptoms in men are painful urination and pus discharge. Blockage of the urethra and sterility are complications of untreated cases.
7. Women might be asymptomatic unless the infection spreads to the uterus and uterine tubes (see pelvic inflammatory disease).
8. Gonorrheal endocarditis, gonorrheal meningitis, and gonorrheal arthritis are complications that can affect both sexes if gonorrheal infections are untreated.
9. Ophthalmia neonatorum is an eye infection acquired by infants during passage through the birth canal of an infected mother.
10. Gonorrhea is diagnosed by ELISA or nucleic acid amplification.

Nongonococcal Urethritis (NGU) (pp. 755–757)

11. Most cases of nongonococcal urethritis (NGU), or nonspecific urethritis (NSU), are caused by *Chlamydia trachomatis*.
12. *C. trachomatis* infection is the most common STI.
13. Symptoms of NGU are often mild or lacking, although uterine tube inflammation and sterility may occur.
14. *C. trachomatis* can be transmitted to infants' eyes at birth.
15. Diagnosis is based on detection of chlamydial DNA in urine.
16. *Ureaplasma urealyticum* and *Mycoplasma hominis* also cause NGU.

Pelvic Inflammatory Disease (PID) (p. 757)

17. Extensive bacterial infection of the female pelvic organs, especially of the reproductive system, is called pelvic inflammatory disease (PID).
18. PID is caused by *N. gonorrhoeae, C. trachomatis,* and other bacteria. Infection of the uterine tubes is called salpingitis.

Syphilis (pp. 757–760)

19. Syphilis is caused by *Treponema pallidum,* a spirochete that has not been cultured in vitro. Laboratory cultures are grown in rabbits or cell cultures.
20. The primary lesion is a small, hard-based chancre at the site of infection. The bacteria then invade the blood and lymphatic system, and the chancre spontaneously heals.
21. The appearance of a widely disseminated rash on the skin and mucous membranes marks the secondary stage. Spirochetes are present in the lesions of the rash.
22. The patient enters a latent period after the secondary lesions spontaneously heal.
23. At least 10 years after the secondary lesion, tertiary lesions called gummas can appear on many organs.
24. Congenital syphilis, resulting from *T. pallidum* crossing the placenta during the latent period, can cause neurological damage in the newborn.
25. *T. pallidum* is identifiable through darkfield microscopy of fluid from primary and secondary lesions.
26. Many serological tests, such as VDRL, RPR, and FTA-ABS, can be used to detect the presence of antibodies against *T. pallidum* during any stage of the disease.

Lymphogranuloma Venereum (LGV) (pp. 760–761)

27. *C. trachomatis* causes lymphogranuloma venereum (LGV), which is primarily a disease of tropical and subtropical regions.
28. The bacteria are spread in the lymph system and cause enlargement of the lymph nodes, obstruction of lymph vessels, and swelling of the external genitals.
29. Diagnosis is usually by detection of antibodies to *C. trachomatis*.

Chancroid (Soft Chancre) (p. 761)

30. Chancroid, a swollen, painful ulcer on the mucous membranes of the genitals or mouth, is caused by *Haemophilus ducreyi.*

Bacterial Vaginosis (pp. 761–762)

31. Bacterial vaginosis is an infection without inflammation caused by *Gardnerella vaginalis.*
32. Diagnosis of *G. vaginalis* is based on increased vaginal pH, fishy odor, and the presence of clue cells.

Viral Diseases of the Reproductive Systems (pp. 762–764)

Genital Herpes (pp. 762–763)

1. Herpes simplex viruses (HSV-1 and HSV-2) cause genital herpes.
2. Symptoms of the infection are painful urination, genital irritation, and fluid-filled vesicles.
3. The virus might enter a latent stage in nerve cells. Vesicles reappear following trauma and hormonal changes.
4. Neonatal herpes is contracted during fetal development or birth. It can result in neurological damage or infant fatalities.

Genital Warts (pp. 763–764)

5. Human papillomaviruses cause warts.
6. Some human papillomaviruses that cause genital warts cause cervical cancer.

AIDS (p. 764)

7. AIDS is a sexually transmitted disease of the immune system (see Chapter 19, pages 534–544).

Fungal Disease of the Reproductive Systems (pp. 764–765)

Candidiasis (p. 765)

1. *Candida albicans* causes NGU in men and vulvovaginal candidiasis, or yeast infection, in women.
2. Vulvovaginal candidiasis is characterized by lesions that produce itching and irritation.
3. Predisposing factors are pregnancy, diabetes, and broad-spectrum antibacterial chemotherapy.
4. Diagnosis is based on observation of the fungus and its isolation from lesions.

Protozoan Disease of the Reproductive Systems (pp. 765–767)

Trichomoniasis (pp. 765–767)

1. *Trichomonas vaginalis* causes trichomoniasis when the pH of the vagina increases.
2. Diagnosis is based on observation of the protozoa in purulent discharges from the site of infection.

The TORCH Panel of Tests (p. 767)

3. Antibodies against specific diseases that can infect a fetus are detected by the TORCH tests.

Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. DRAW IT Diagram the pathway taken by *E. coli* to cause cystitis. Do the same for pyelonephritis. Diagram the pathway taken by *Neisseria gonorrhoeae* to cause PID.



2. How are urinary tract infections transmitted?
3. Explain why *E. coli* is frequently implicated in cystitis in females. List some predisposing factors for cystitis.
4. Name one organism that causes pyelonephritis. What are the portals of entry for microbes that cause pyelonephritis?
5. Complete the following table:

Disease	Causative Agent	Symptoms	Method of Diagnosis	Treatment
Bacterial vaginosis				
Gonorrhea				
Syphilis				
PID				
NGU				
LGV				
Chancroid				

6. Describe the symptoms of genital herpes. What is the causative agent? When is this infection least likely to be transmitted?
7. Name one fungus and one protozoan that can cause reproductive system infections. What symptoms would lead you to suspect these infections?
8. List the genital infections that cause congenital and neonatal infections. How can transmission to a fetus or newborn be prevented?
9. NAME IT Intracellular reticulate bodies of this gram-negative bacterium convert to elementary bodies that can infect a new host cell.

Multiple Choice

1. Which of the following is usually transmitted by contaminated water?
   a. *Chlamydia*
   b. leptospirosis
   c. syphilis
   d. trichomoniasis
   e. none of the above

Use the following choices to answer questions 2–5:
a. *Candida*
b. *Chlamydia*
c. *Gardnerella*
d. *Neisseria*
e. *Trichomonas*

2. Microscopic examination of vaginal smear shows flagellated eukaryotes.
3. Microscopic examination of vaginal smear shows ovoid eukaryotic cell.
4. Microscopic examination of vaginal smear shows epithelial cells covered with bacteria.
5. Microscopic examination of vaginal smear shows gram-negative cocci in phagocytes.

Use the following choices to answer questions 6–8:
a. candidiasis
b. bacterial vaginosis
c. genital herpes
d. lymphogranuloma venereum
e. trichomoniasis

6. Difficult to treat with chemotherapy
7. Fluid-filled vesicles
8. Frothy, fishy discharge

Use the following choices to answer questions 9 and 10:
a. *Chlamydia trachomatis*
b. *Escherichia coli*
c. *Mycobacterium hominis*
d. *Staphylococcus saprophyticus*

9. The most common cause of cystitis
10. In cases of NGU, diagnosis is made using PCR to detect microbial DNA.

Analysis

1. The tropical skin disease called yaws is transmitted by direct contact. Its causative agent, *Treponema pallidum pertenue,* is indistinguishable from *T. pallidum.* Syphilis epidemics in Europe coincided with the return of Columbus from the New World. How might *T. pallidum pertenue* have evolved into *T. pallidum* in the temperate climate of Europe?
2. Why can frequent douching be a predisposing factor to bacterial vaginosis, vulvovaginal candidiasis, or trichomoniasis?
3. *Neisseria* is cultured on Thayer-Martin media, consisting of chocolate agar and nystatin, incubated in a 5% CO_2 environment. How is this selective for *Neisseria*?

4. The list below is a key to selected microorganisms that cause genitourinary infections. Complete this key by listing genera discussed in this chapter in the blanks that correspond to their respective characteristics.

Gram-negative bacteria
- Spirochete
  - Aerobic : a. _____
  - Anaerobic : b. _____
- Coccus
  - Oxidase-positive : c. _____
- Bacillus, nonmotile
  - Requires X factor : d. _____
  - Gram-positive wall : e. _____
- Obligate intracellular parasite : f. _____
- Lacking cell wall
  - Urease-positive : g. _____
  - Urease-negative : h. _____
- Fungus
  - Pseudohyphae : i. _____
- Protozoa
  - Flagella : j. _____
- No organism observed/cultured from patient : k. _____

Clinical Applications and Evaluation

1. A previously healthy 19-year-old woman was admitted to a hospital after 2 days of nausea, vomiting, headache, and neck stiffness. Cerebrospinal fluid and cervical cultures showed gram-negative diplococci in leukocytes; a blood culture was negative. What disease did she have? How was it probably acquired?

2. A 28-year-old woman was admitted to a Wisconsin hospital with a 1-week history of arthritis of the left knee. Four days later, a 32-year-old man was examined for a 2-week history of urethritis and a swollen, painful left wrist. A 20-year-old woman seen in a Philadelphia hospital had pain in the right knee, left ankle, and left wrist for 3 days. Pathogens cultured from synovial fluid or urethral culture were gram-negative diplococci that required proline to grow. Antibiotic sensitivity tests gave the following results:

Antibiotic	MIC Tested (μg/ml)	Susceptible MIC (μg/ml)
Cefoxitin	0.5	≤2
Penicillin	8	≤0.06
Spectinomycin	64	≤32
Tetracycline	4	≤0.25

What is the pathogen, and how is this disease transmitted? Which of the antibiotics should be used for treatment? What is the evidence that these cases are related?

3. Using the following information, determine what the disease is and how the infant's illness might have been prevented:

May 11: A 23-year-old woman has her first prenatal examination. She is $4\frac{1}{2}$ months pregnant. Her VDRL results are negative.

June 6: The woman returns to her physician complaining of a labial lesion of a few days' duration. A biopsy is negative for malignancy, and herpes test results are negative.

July 1: The woman returns to her physician because the labial lesion continues to cause some discomfort.

Sept. 15: The baby's father has multiple penile lesions and a generalized body rash.

Sept. 25: The woman delivers her baby. Her RPR is 32, and the infant's is 128.

Oct. 1: The woman takes her infant to a pediatrician because the baby is lethargic. She is told the infant is healthy and not to worry.

Oct. 2: The baby's father has a persistent body rash and plantar and palmar rashes.

Nov. 8: The infant becomes acutely ill with pneumonia and is hospitalized. The admitting physician finds signs of osteochondritis.



In the Clinic

As an environmental health nurse, you are investigating ways to reduce nitrous oxide (N_2O) levels in the atmosphere. Global warming is a public health concern, and N_2O is a greenhouse gas that can absorb 300 times more radiant energy than carbon dioxide. You know that nitrate fertilizers are essential for crops but that N_2O emissions are linked to soil nitrite levels. In your experiments, fertilizer with microbial inhibitors was associated with lower N_2O levels than was fertilizer without inhibitors. **Explain why the microbial inhibitors reduced N_2O production.**

Hint: Read about the nitrogen cycle on pages 774–776.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

27 Environmental Microbiology

In previous chapters, we focused primarily on the disease-causing capabilities of microorganisms. Environmental health microbiologists test drinking water regularly to ensure that it is free of pathogens. One such pathogen, *Vibrio cholerae,* shown in the photo, is the topic of the Clinical Case in this chapter. You will also learn about many of the positive functions microbes perform in the environment. Bacteria and other microorganisms are, in fact, essential to maintaining life on Earth.

Microbes, especially those that belong to the Domains Bacteria and Archaea, live in the most widely varied habitats on Earth. They are found in boiling hot springs, and as many as 5000 bacteria have been isolated from each milliliter of snow at the South Pole. Microbes have been recovered from minute openings in rocks a kilometer (0.62 mile) or more below the planet surface. Explorations of the deepest ocean have revealed large numbers of microbes living there, in eternal darkness and subject to incredible pressures. Microbes are also found in clear mountain streams flowing from a melting glacier and in waters nearly saturated with salts, such as those of the Dead Sea.

Vibrio cholerae.

Microbial Diversity and Habitats

LEARNING OBJECTIVES

27-1 Define *extremophile,* and identify two "extreme" habitats.

27-2 Define *symbiosis*.

27-3 Define *mycorrhiza,* differentiate endomycorrhizae from ectomycorrhizae, and give an example of each.

The diversity of microbial populations indicates that they take advantage of any niches found in their environment. Different amounts of oxygen, light, or nutrients may exist within a few millimeters in the soil. As a population of aerobic organisms uses up the available oxygen, anaerobes are able to grow. If the soil is disturbed by plowing, earthworms, or other activity, the aerobes will again be able to grow to repeat this succession.

ASM: Microorganisms and their environment interact with and modify each other.

Microbes that live in extreme conditions of temperature, acidity, alkalinity, or salinity are called **extremophiles.** Most are members of the Archaea. The enzymes (**extremozymes**) that make growth possible under these conditions have been of great interest to industries because they can tolerate extremes of temperature, salinity, and pH that would inactivate other enzymes.

Microorganisms live in an intensely competitive environment and must exploit any advantage they can. They may metabolize common nutrients more rapidly or use nutrients that competing organisms cannot metabolize. Some, such as the lactic acid bacteria that are so useful in making dairy products, are able to make an environmental niche inhospitable to competing organisms. The lactic acid bacteria are unable to use oxygen as an electron acceptor and are able to ferment sugars only to lactic acid, leaving most of the energy unused. However, the acidity inhibits the growth of more efficient, competing microbes.

Symbiosis

Symbiosis is a close association between two unlike organisms that is beneficial to one or both of them (recall Chapter 14). Economically, the most important example of an animal-microbe symbiosis is that of the ruminants, animals that have a tank-like digestive organ called a *rumen.* Ruminants, such as cattle and sheep, graze on cellulose-rich plants. Bacteria in the rumen ferment the cellulose into compounds that are absorbed into the animal's blood and subsequently are used for carbon and energy. Rumen protozoa keep the bacterial population under control by eating bacteria.

Another important example of symbiosis is the relationship between plant roots and certain fungi, called **mycorrhizae,** or mycorrhizal symbionts (*myco* = fungus; *rhiza* = root). There are two primary types of these fungi: *endomycorrhizae,* also known as *arbuscular mycorrhizae;* and *ectomycorrhizae.* Both types function as do root hairs on plants; that is, they extend the surface area through which the plant can absorb nutrients, especially phosphorus, which is not very mobile in soil.



(a) Mycorrhizal infection influences the growth of many plants. The pine seedling on the left was inoculated with mycorrhizae; the seedling on the right was not.

(b) Truffles. An ectomycorrhiza, usually of oak trees.

Figure 27.1 Mycorrhizae and their considerable commercial value.

Q Why are mycorrhizae valuable for the uptake of phosphorus?

Most grasses and other plants are surprisingly dependent on these fungi for proper growth, and their presence is nearly universal in the plant kingdom. Managers of commercial pine tree farms, for example, must ensure that seedlings are inoculated with soil containing effective mycorrhizae (**Figure 27.1a**).

Truffles, known as a food delicacy, are ectomycorrhizae, usually of oak trees (Figure 27.1b). Biologists consider them an "underground mushroom"—mushrooms that have developed a different, nonaerial method of distributing their spores. This distribution depends upon the truffles' ability to attract the attention of animals that will ingest them and then deposit undigested spores into new locations.

CHECK YOUR UNDERSTANDING

- Identify two habitats for extremophile organisms. **27-1**
- What is the definition of *symbiosis?* **27-2**
- Is a truffle an endomycorrhiza or an ectomycorrhiza? **27-3**

Soil Microbiology and Biogeochemical Cycles

LEARNING OBJECTIVES

27-4 Define *biogeochemical cycle*.

27-5 Outline the carbon cycle, and explain the roles of microorganisms in this cycle.

27-6 Outline the nitrogen cycle, and explain the roles of microorganisms in this cycle.

27-7 Define *ammonification, nitrification, denitrification,* and *nitrogen fixation*.

27-8 Outline the sulfur cycle, and explain the roles of microorganisms in this cycle.

27-9 Describe how an ecological community can exist without light.

27-10 Compare and contrast the carbon cycle and the phosphorus cycle.

27-11 Give two examples of the use of bacteria to remove pollutants.

27-12 Define *bioremediation*.

Billions of organisms, including microbes as well as comparatively huge insects and earthworms, form a vibrant living community in the soil. Typical soil has millions of bacteria in each gram. One gram of soil might seem to be a small sample, but it can yield some startling statistics. Estimates are that it would have 20,000 square meters of surface area. Bacterial numbers in this sample would be about 1 billion (although only about 1% can be cultured), and it might contain more than a kilometer of fungal hyphae. Even so, only a very tiny fraction of the available surface area in that gram of soil is colonized by microbes. The microbial population of soil is largest in the top few centimeters and declines rapidly with depth. The most numerous organisms in soil are bacteria. Although actinomycetes are bacteria, they are usually considered separately.

Bacterial soil populations are usually estimated using plate counts on nutrient media, and the actual numbers are probably greatly underestimated by this method. No single nutrient medium or growth condition can possibly meet all the nutritional and other requirements of soil microorganisms.

We can think of soil as a "biological fire." A leaf falling from a tree is consumed by this fire as microbes in the soil metabolize its organic matter. Elements in the leaf enter the **biogeochemical cycles** for carbon, nitrogen, and sulfur that we will discuss in this chapter. In biogeochemical cycles, elements are oxidized and reduced by microorganisms to meet their metabolic needs. (See the discussion of oxidation-reduction in Chapter 5, pages 117–118.) Without biogeochemical cycles, life on Earth would cease to exist.

The Carbon Cycle

The primary biogeochemical cycle is the **carbon cycle** (Figure 27.2). All organisms, including plants, microbes, and animals, contain large amounts of carbon in the form of organic compounds such as cellulose, starches, fats, and proteins. Let's take a closer look at how these organic compounds are formed.

Recall from Chapter 5 that autotrophs perform an essential role for all life on Earth by reducing carbon dioxide to form organic matter. When you look at a tree, you might think that its mass has come from the soil where it grows. In fact, its great mass of cellulose is derived from the 0.03% of carbon dioxide in the atmosphere. This occurs as a result of photosynthesis, the first step of the carbon cycle in which photoautotrophs *fix* (incorporate) carbon dioxide into organic matter using energy from sunlight.

In the next step of the cycle, chemoheterotrophs such as animals and protozoa eat autotrophs and may in turn be eaten by other animals. Thus, as the organic compounds of the autotrophs are digested and resynthesized, the carbon atoms of carbon dioxide are transferred from organism to organism up the food chain.

Chemoheterotrophs, including animals, use some of the organic molecules to satisfy their energy requirements. When this energy is released through respiration, carbon dioxide immediately becomes available to start the cycle over again. Much of the carbon remains within the organisms until they excrete it as wastes or die. When plants and animals die, these organic compounds are decomposed by bacteria and fungi. During decomposition, the organic compounds are oxidized, and CO_2 is returned to the cycle.

Carbon is stored in rocks, such as limestone ($CaCO_3$), and is dissolved as carbonate ions (CO_3^{2-}) in oceans. Vast deposits of fossil organic matter exist in the form of fossil fuels, such as coal and petroleum. Burning these fossil fuels releases CO_2, increasing the amount of CO_2 in the atmosphere. This increased atmospheric carbon dioxide may be causing a **global warming** of the Earth.

An interesting aspect of the carbon cycle is methane (CH_4) gas. Sediments on the ocean floor contain an estimated 10 trillion tons of methane, about twice as much as the Earth's deposits of fossil fuels such as coal and petroleum. Furthermore, methanogenic bacteria in the ocean's depths are constantly producing more (see page 780). Methane is much more potent as a greenhouse gas than is carbon dioxide, and the Earth's environment would be dangerously altered if all this gas escaped to the atmosphere.

CHECK YOUR UNDERSTANDING

- What biogeochemical cycle is much publicized as contributing to global warming? **27-4**
- What is the main source of the carbon in the cellulose forming the mass of a forest? **27-5**

Clinical Case: Clean Water—A Matter of Life and Death

Two days ago, Charity, a 48-year-old journalist from Miami, returned to the United States from a 6-week trip to several countries for a story she is writing on recovery progress after major earthquakes. When she first came home, Charity began to experience diarrhea, which became worse as the day progressed. After the second day of severe diarrhea and the beginning of leg pain, Charity seeks care at a local outpatient health care facility. She reports no vomiting or fever but has 10 watery stools per day without visible blood or mucus.

What immediate treatment does Charity need? Read on to find out.

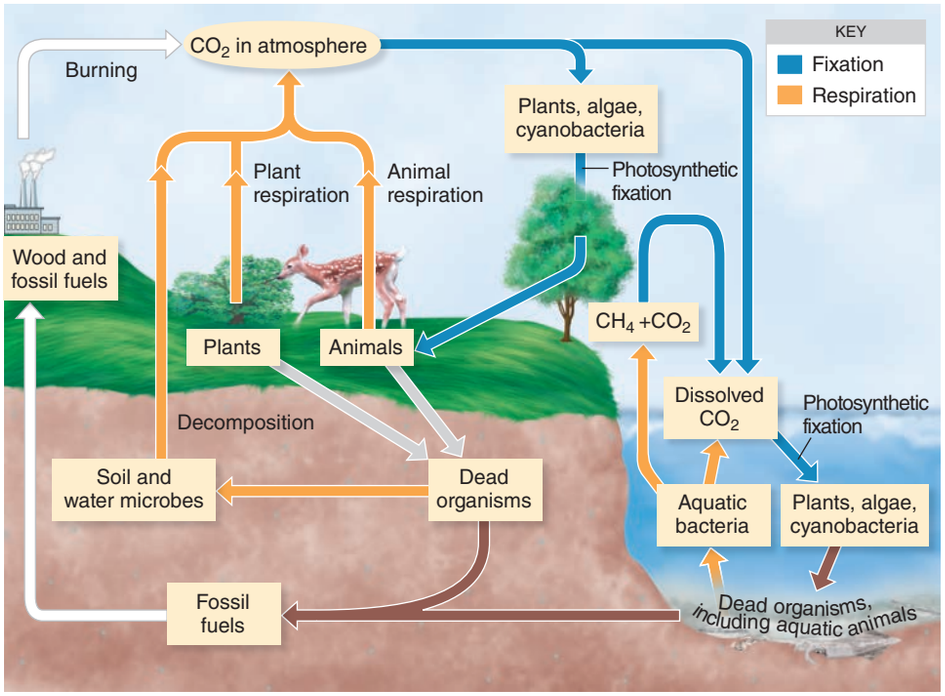


Figure 27.2 The carbon cycle. On a global scale, the return of CO_2 to the atmosphere by respiration closely balances its removal by fixation. However, the burning of wood and fossil fuels adds more CO_2 to the atmosphere. The destruction of forests and wetlands removes CO_2-fixing organisms; as a result, the amount of atmospheric CO_2 is steadily increasing.

Q How does the accumulation of carbon dioxide in the atmosphere affect Earth's climate?

The Nitrogen Cycle

The **nitrogen cycle** is shown in Figure 27.3. All organisms need nitrogen to synthesize protein, nucleic acids, and other nitrogen-containing compounds. Molecular nitrogen (N_2) makes up almost 80% of the Earth's atmosphere. For plants to assimilate and use nitrogen, it must be fixed, that is, taken up and combined into organic compounds. The activities of specific microorganisms are important to the conversion of nitrogen to usable forms.

Ammonification

Almost all the nitrogen in the soil exists in organic molecules, primarily in proteins. When an organism dies, the process of microbial decomposition results in the hydrolytic breakdown of proteins into amino acids. In a process called **deamination,** the amino groups of amino acids are removed and converted into ammonia (NH_3). This release of ammonia is called **ammonification** (see Figure 27.3). Ammonification, brought about by numerous bacteria and fungi, can be represented as follows:

$$\text{Proteins form dead cells and waste products} \xrightarrow{\text{Microbial decomposition}} \text{Amino acids}$$

$$\text{Amino acids} \xrightarrow{\text{Microbial decomposition}} \text{Ammonia } (NH_3)$$

Microbial growth releases extracellular proteolytic enzymes that decompose proteins. The resulting amino acids are transported into the microbial cells, where ammonification occurs. The fate of the ammonia produced by ammonification depends on soil conditions (see the discussion of denitrification, which follows). Because ammonia is a gas, it rapidly disappears from dry soil, but in moist soil it becomes solubilized in water, and ammonium ions (NH_4^+) are formed:

$$NH_3 + H_2O \longrightarrow NH_4^+OH \longrightarrow NH_4^+OH^-$$

Ammonium ions from this sequence of reactions are used by bacteria and plants for amino acid synthesis.

Nitrification

The next sequence of reactions in the nitrogen cycle involves the oxidation of the nitrogen in the ammonium ion to produce nitrate, a process called **nitrification.** Living in the soil are autotrophic nitrifying bacteria, such as those of the genera *Nitrosomonas* and *Nitrobacter*. These microbes obtain energy by oxidizing ammonia or nitrite. In the first stage, *Nitrosomonas* oxidizes ammonium to nitrites:

$$\underset{\text{Ammonium ion}}{NH_4^+} \xrightarrow{\textit{Nitrosomonas}} \underset{\text{Nitrate ion}}{NO_2^-}$$

In the second stage, such organisms as *Nitrobacter* oxidize nitrites to nitrates:

$$\underset{\text{Nitrite ion}}{NO_2^-} \xrightarrow{\textit{Nitrobacter}} \underset{\text{Nitrate ion}}{NO_3^-}$$

Plants tend to use nitrate as their source of nitrogen for protein synthesis because nitrate is highly mobile in soil and is more likely than ammonium to encounter a plant root. Ammonium ions would actually make a more efficient source of nitrogen because

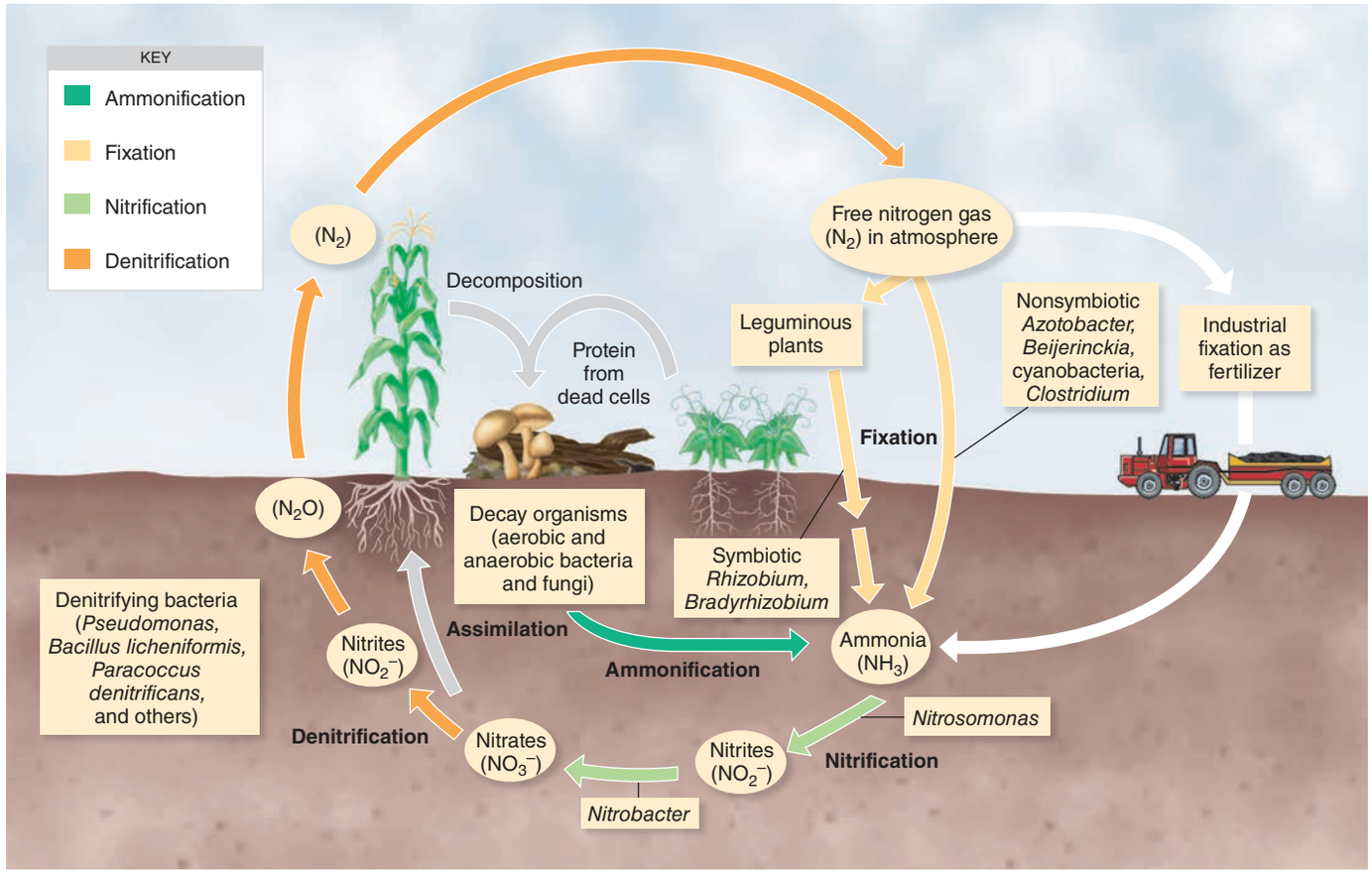


Figure 27.3 The nitrogen cycle. In general, nitrogen in the atmosphere goes through fixation, nitrification, and denitrification. Nitrates assimilated into plants and animals after nitrification go through decomposition, ammonification, and then nitrification again.

Q Which processes are performed exclusively by bacteria?

they require less energy to incorporate into protein, but these positively charged ions are usually bound to negatively charged clays in the soil, whereas the negatively charged nitrate ions are not bound.

Denitrification

The form of nitrogen resulting from nitrification is fully oxidized and no longer contains any biologically usable energy. However, it can be used as an electron acceptor by microbes metabolizing other organic energy sources in the absence of atmospheric oxygen (see the discussion of anaerobic respiration on pages 126–127). This process, called **denitrification,** can lead to a loss of nitrogen to the atmosphere, especially as nitrogen gas. Denitrification can be represented as follows:

$$\underset{\text{Nitrate ion}}{NO_3^-} \longrightarrow \underset{\text{Nitrate ion}}{NO_2^-} \longrightarrow \underset{\text{Nitrous oxide}}{N_2O} \longrightarrow \underset{\text{Nitrous gas}}{N_2}$$

Denitrification occurs in waterlogged soils, where little oxygen is available. In the absence of oxygen as an electron acceptor, denitrifying bacteria substitute the nitrates of agricultural fertilizer. This converts much of the valuable nitrate into gaseous nitrogen that enters the atmosphere and represents a considerable economic loss.

Nitrogen Fixation

We live at the bottom of an ocean of nitrogen gas. The air we breathe is about 79% nitrogen, and above every acre of soil (the area of an American football field from the goal line to the opposite 10-yard line, or 50.6 × 80 meters) stands a column of nitrogen weighing about 32,000 tons. But only a few species of bacteria, including cyanobacteria, can use it directly as a nitrogen source. The process by which they convert nitrogen gas to ammonia is known as **nitrogen fixation.**

Bacteria that are responsible for nitrogen fixation all rely on the same enzyme, *nitrogenase.* It is estimated that Earth's entire supply of this essential enzyme could fit into a single large bucket. Nitrogenase is inactivated by oxygen. Therefore, it probably evolved early in the history of the planet, before the atmosphere contained much molecular oxygen and before nitrogen-containing compounds were available from decaying

organic matter. Nitrogen fixation is brought about by two types of microorganisms: free-living and symbiotic. (Agricultural fertilizers are made up of nitrogen that has been fixed by industrial physical–chemical processes.)

Free-Living Nitrogen-Fixing Bacteria Free-living nitrogen-fixing bacteria are found in particularly high concentrations in the *rhizosphere,* a region roughly 2 millimeters from the plant root. The rhizosphere represents something of a nutritional oasis in the soil, especially in grasslands. Among the free-living bacteria that can fix nitrogen are aerobic species such as *Azotobacter.* These aerobic organisms apparently shield the anaerobic nitrogenase enzyme from oxygen by, among other things, having a very high rate of oxygen use that minimizes the diffusion of oxygen into the interior of the cell, where the enzyme is located.

Another free-living obligate aerobe that fixes nitrogen is *Beijerinckia* (bī-yer-INK-ē-ah). Some anaerobic bacteria, such as certain species of *Clostridium* (klos-TRID-ē-um), also fix nitrogen. The bacterium *C. pasteurianum* (PAS-tyer-ē-ā-num), an obligately anaerobic, nitrogen-fixing microorganism, is a prominent example.

There are many species of aerobic, photosynthesizing cyanobacteria that fix nitrogen. Because their energy supply is independent of carbohydrates in soil or water, they are especially useful suppliers of nitrogen to the environment. Cyanobacteria usually carry their nitrogenase enzymes in specialized structures called **heterocysts** that provide anaerobic conditions for fixation (see Figure 11.13, page 303).

Most of the free-living nitrogen-fixing bacteria are capable of fixing large amounts of nitrogen under laboratory conditions. However, in the soil there is usually a shortage of usable carbohydrates to supply the energy needed to reduce nitrogen to ammonia, which is then incorporated into protein. Nevertheless, these nitrogen-fixing bacteria make important contributions to the nitrogen economy of such areas as grasslands, forests, and the arctic tundra.

Symbiotic Nitrogen-Fixing Bacteria Symbiotic nitrogen-fixing bacteria play an even more important role in plant growth for crop production. Members of the genera *Rhizobium, Bradyrhizobium,* and others infect the roots of leguminous plants, such as soybeans, beans, peas, peanuts, alfalfa, and clover. (These agriculturally important plants are only a few of the thousands of known leguminous species, many of which are bushy plants or small trees found in poor soils in many parts of the world.) Rhizobia, as these bacteria are commonly known, are specially adapted to particular leguminous plant species, on which they form **root nodules** (Figure 27.4). Nitrogen is then fixed by a symbiotic process of the plant and the bacteria. The plant furnishes anaerobic conditions and growth nutrients for the bacteria, and the bacteria fix nitrogen that can be incorporated into plant protein.

There are similar examples of symbiotic nitrogen fixing *Frankia* in nonleguminous plants, such as alder trees. The growth of 1 acre of alder trees can fix about 50 kg of nitrogen each year; the trees thus make a valuable addition to the forest economy.

Another important contribution to the nitrogen economy of forests is made by **lichens,** which are a combination of fungus and an alga or a cyanobacterium in a mutualistic relationship (see Figure 12.11, page 332). When one symbiont is a nitrogen-fixing cyanobacterium, the product is fixed nitrogen that eventually enriches the forest soil. Free-living cyanobacteria can fix significant amounts of nitrogen in desert soils after rains and on the surface of arctic tundra soils. Rice paddies can accumulate heavy growths of such nitrogen-fixing organisms. The cyanobacteria also form a symbiosis with a small floating fern, *Azolla,* which grows thickly in rice paddy waters (Figure 27.5).

CHECK YOUR UNDERSTANDING

- What is the common name for the group of microbes that oxidize soil nitrogen into a form that is mobile in soil and likely to be used by plants for nutrition? **27-6**
- Bacteria of the genus *Pseudomonas,* in the absence of oxygen, will use fully oxidized nitrogen as an electron acceptor, a process in the nitrogen cycle that is given what name? **27-7**

The Sulfur Cycle

The **sulfur cycle** (Figure 27.6) and nitrogen cycle resemble each other in the sense that they represent numerous oxidation states of these elements. The most reduced forms of sulfur are the sulfides, such as the odorous gas hydrogen sulfide (H_2S). Like the ammonium ion of the nitrogen cycle, this is a reduced compound that generally forms under anaerobic conditions. In turn it represents a source of energy for autotrophic bacteria. These bacteria convert the reduced sulfur in H_2S into elemental sulfur granules and fully oxidized sulfates (SO_4^{2-}).

Several phototrophic bacteria, such as the green and purple sulfur bacteria, also oxidize H_2S, forming colorful internal sulfur granules (see Figure 11.14, page 304). Like *Beggiatoa,* they can further oxidize the sulfur to sulfate ions. It is important to recognize that these organisms are using light for energy; the hydrogen sulfide is used to reduce CO_2 (see Chapter 5, page 133).

Plants and bacteria incorporate sulfates to become part of sulfur-containing amino acids for humans and other animals. There, they form disulfide links that give structure to proteins. As proteins are decomposed, in a process called **dissimilation,** the sulfur is released as hydrogen sulfide to reenter the cycle.

Life without Sunshine

Interestingly, it is possible for entire biological communities to exist without photosynthesis by exploiting the energy in H_2S. Chapter 11 (page 304) presents equations to show that photosynthesis and chemoautotrophic use of H_2S are similar in certain respects. Such communities occur, for example,

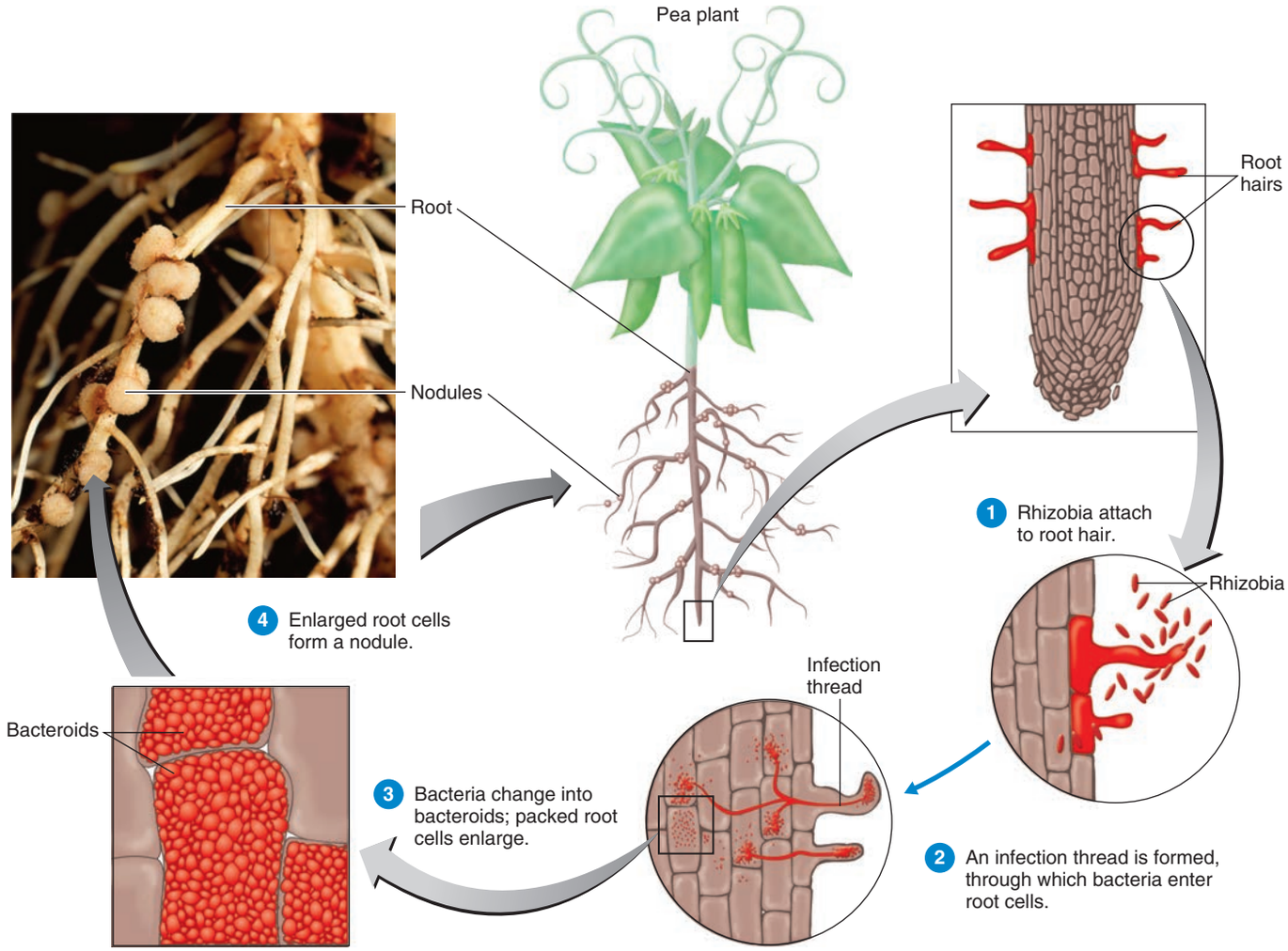


Figure 27.4 The formation of a root nodule. Members of the nitrogen-fixing genera *Rhizobium* and *Bradyrhizobium* form these nodules on legumes. This mutualistic association is beneficial to both the plant and the bacteria.

Q In nature, are leguminous plants more likely to be valuable in rich agricultural soils or in poor desert soils?

around deep-sea vents. Deep caves, totally isolated from sunlight, have been discovered that also support entire biological communities. The **primary producers** in these systems are chemoautotrophic bacteria rather than photoautotrophic plants or microbes.

Recently another microbial ecosystem operating far from sunlight has been discovered over 1 km deep within rocks, including shales, granites, and basalts. Such bacteria are called **endoliths** (inside rocks), which must grow in the near absence of oxygen and with minimal nutrient supplies. Carbon dioxide dissolved in the water serves as a carbon source, and cellular organic matter is produced. Some is excreted, or is released upon the death and lysis of the microbe, and becomes available for the growth of other microbes. Nutrient inputs, especially

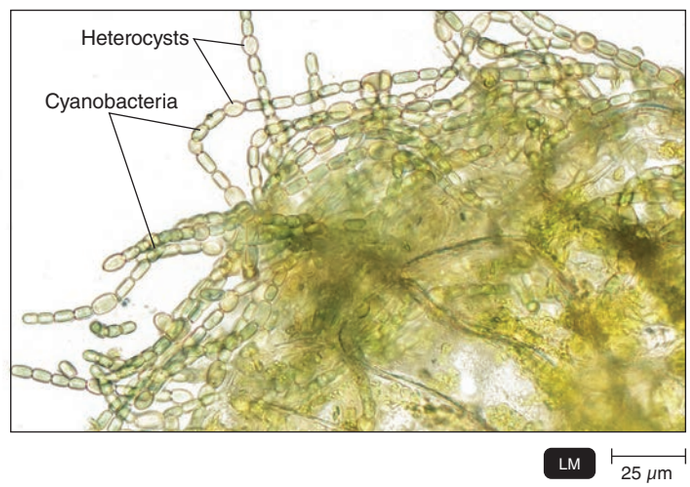


Figure 27.5 The *Azolla*–cyanobacteria symbiosis. A section through the leaf of an *Azolla* freshwater fern. The cyanobacterium *Anabaena azollae* is visible as chains of cells within the leaf cavity.

Q What is the major contribution of cyanobacteria as symbionts?

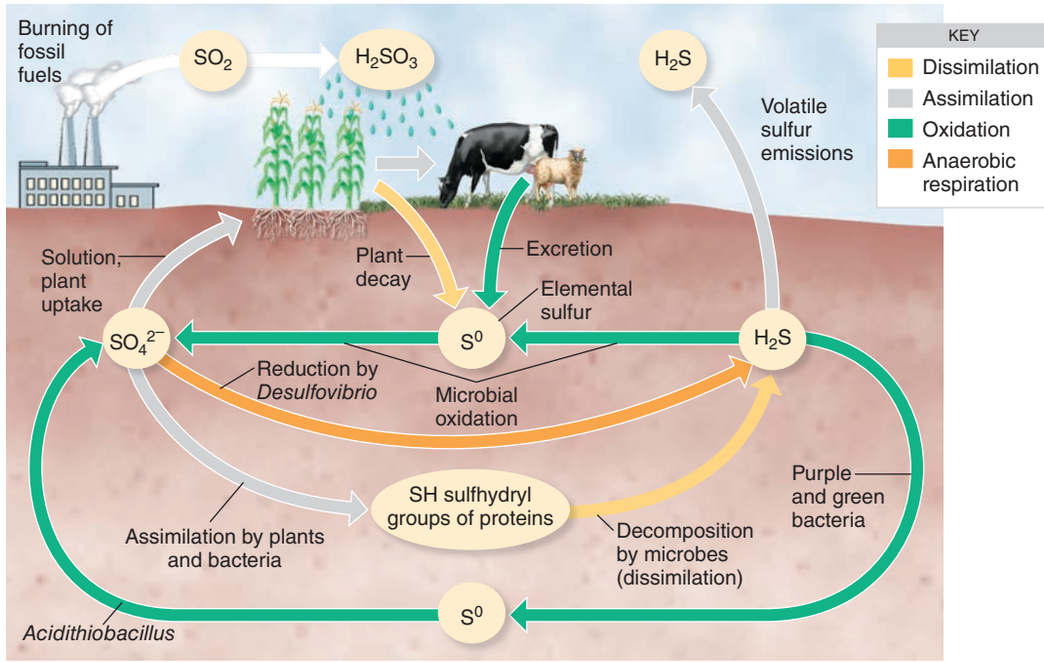


Figure 27.6 The sulfur cycle. Reduced forms of sulfur such as H_2S and elemental sulfur (S°) are energy sources for some microbes under aerobic or anaerobic conditions. Under anaerobic conditions, H_2S can be used as a substitute for H_2O in photosynthesis by purple and green bacteria (see page 304) to produce S°. Oxidized forms of sulfur, such as sulfates (SO_4^{2-}), are used as electron acceptors, as a substitute for oxygen, under anaerobic conditions by certain bacteria. Many organisms assimilate sulfates to make the —SH groups of proteins.

Q Why is a source of sulfur necessary for all organisms?

nitrogen, are very small in this environment, and generation times may be measured in many years.

The Phosphorus Cycle

Another important nutritional element that is part of a biogeochemical cycle is phosphorus. The availability of phosphorus may determine whether plants and other organisms can grow in an area. The problems associated with excess phosphorus (eutrophication) are described later in the chapter.

Phosphorus exists primarily as phosphate ions (PO_4^{3-}) and undergoes very little change in its oxidation state. The **phosphorus cycle** instead involves changes from soluble to insoluble forms and from organic to inorganic phosphate, often in relation to pH. For example, phosphate in rocks can be solubilized by the acid produced by bacteria such as *Acidithiobacillus*. Unlike the other cycles, there is no volatile phosphorus-containing product to return phosphorus to the atmosphere in the way carbon dioxide, nitrogen gas, and sulfur dioxide are returned. Therefore, phosphorus tends to accumulate in the seas. It can be retrieved by mining the above-ground sediments of ancient seas, mostly as deposits of calcium phosphate. Seabirds also mine phosphorus from the sea by eating phosphorus-containing fish and depositing it as guano (bird droppings). Certain small islands inhabited by such birds have long been mined for these deposits as a source of phosphorus for fertilizers.

CHECK YOUR UNDERSTANDING

- Certain nonphotosynthetic bacteria accumulate granules of sulfur within the cell; are the bacteria using hydrogen sulfide or sulfates as an energy source? **27-8**
- What chemical usually serves as an energy source for organisms that survive in darkness? **27-9**
- Why does phosphorus tend to accumulate in the seas? **27-10**

The Degradation of Synthetic Chemicals in Soil and Water

We take for granted that soil microorganisms will degrade materials entering the soil. Natural organic matter, such as falling leaves or animal residues, is in fact readily degraded. However, in this industrial age many chemicals that do not occur in nature (**xenobiotics**), such as plastics, enter the soil in large amounts. In fact, plastics comprise about a fourth of all municipal wastes. A proposed solution to the problem is to develop biodegradable plastics made from polylactide (PLA) produced by lactic acid fermentation. When composted (see Figure 27.8 on facing page), PLA plastic degrades in a few weeks. PLA-based plastics are appearing in a number of commercial products, such as disposable water bottles and drinking cups. Another version of biodegradable plastic, also made from fermented corn sugars, is called polyhydroxyalkanoate, or PHA. Products made of PHA (Mirel) degrade more easily and can stand higher temperatures in use, but they are more expensive than PLA. Many synthetic chemicals, such as pesticides, are highly resistant to degradation by microbial attack. A well-known example is the insecticide DDT, which proved so resistant that it accumulated to damaging levels in the environment.

Small differences in chemical structure can make large differences in biodegradability. The classic example is that of two herbicides: 2,4-D (the common chemical used to kill lawn weeds) and 2,4,5-T (used to kill shrubs); both were components

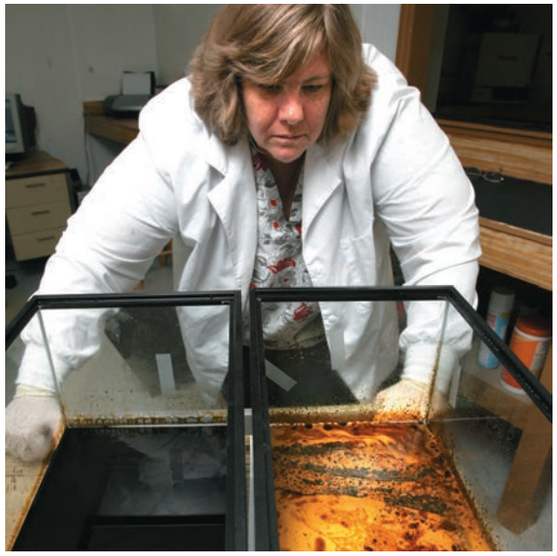


Figure 27.7 Bioremediation of an oil spill in Alaska. A lab manager studies "before" and "after" tanks of oily water from the Gulf oil spill. The tank on the right is the water after 30 days of reduction by oil-eating bacteria.

Q Does the chemical formula of most petroleum products contain nitrogen, or phosphorus? (*Hint:* See the Applications of Microbiology box on page 31 in Chapter 2.)

of Agent Orange, which was used to defoliate jungles during the Vietnam war. The addition of a single chlorine atom to the structure of 2,4-D extends its life in soil from a few days to an indefinite period.

A growing problem is the leaching into groundwaters of toxic materials that are not biodegradable or that degrade very slowly. The sources of these materials may include landfills, illegal industrial dumps, or pesticides applied to agricultural crops.

Bioremediation

The use of microbes to detoxify or degrade pollutants is called **bioremediaton.** Oil spills from wrecked tankers and drilling accidents represent some of the most dramatic examples of chemical pollution. Bioremediation occurs naturally as microbes attack the petroleum if conditions are aerobic. However, microbes usually obtain their nutrients in aqueous solution, and oil-based products are relatively nonsoluble. Also, petroleum hydrocarbons are deficient in essential elements, such as nitrogen and phosphorus. Bioremediation of oil spills is greatly enhanced if the resident bacteria are provided with "fertilizer" containing nitrogen and phosphorus (Figure 27.7). Bioremediaton may also make use of microbes that have been selected for growth on a certain pollutant or of genetically modified bacteria that are specially adapted to metabolize petroleum products. The addition of such specialized microbes is called **bioaugmentation** (see the Applications of Microbiology box in Chapter 2, page 31).

Solid Municipal Waste

Solid municipal waste (garbage) is most frequently placed into large compacted landfills. Conditions are largely anaerobic, and even presumably biodegradable materials such as paper are not very effectively attacked by microorganisms. In fact, recovering a 20-year-old newspaper in readable condition is not at all unusual. But such anaerobic conditions promote activity of the same methanogens used in the operation of anaerobic sludge digesters to treat sewage (see page 787). The methane produced can be tapped with drill holes and burned to generate electricity or purified and introduced into natural gas pipeline systems (see Figure 28.11, page 806). Such systems are part of the design of many large landfills in the U.S., some of which provide energy for industrial plants and homes.

Composting is a process gardeners use to convert plant remains into the equivalent of natural humus. A pile of leaves or grass clippings will undergo microbial degradation. Under favorable conditions, thermophilic bacteria will raise the temperature of the compost to 55–60°C in a couple of days. After the temperature declines, the pile can be turned to renew the oxygen supply, and a second temperature rise will occur. Over time, the thermophilic microbial populations are replaced by mesophilic populations that slowly continue the conversion to a stable material similar to humus. Where space is available, municipal wastes are composted in windrows (long, low piles) that are distributed and periodically turned over by specialized machinery (Figure 27.8). Municipal waste disposal now also makes increasing use of composting methods.

CHECK YOUR UNDERSTANDING

- Why are petroleum products naturally resistant to metabolism by most bacteria? **27-11**
- What is the definition of the term *bioremediation*? **27-12**



Solid municipal wastes being turned by a specially designed machine

Figure 27.8 Composting municipal wastes.

Q A compost pile of grass and leaves is very high in carbon; does it have much nitrogen?

Aquatic Microbiology and Sewage Treatment

LEARNING OBJECTIVES

- **27-13** Describe the freshwater and seawater habitats of microorganisms.
- **27-14** Explain how wastewater pollution is a public health problem and an ecological problem.
- **27-15** Discuss the causes and effects of eutrophication.
- **27-16** Explain how water is tested for bacteriological purity.
- **27-17** Describe how pathogens are removed from drinking water.
- **27-18** Compare primary, secondary, and tertiary sewage treatment.
- **27-19** List some of the biochemical activities that take place in an anaerobic sludge digester.
- **27-20** Define *biochemical oxygen demand (BOD), activated sludge system, trickling filter, septic tank,* and *oxidation pond.*

Aquatic microbiology refers to the study of microorganisms and their activities in natural waters, such as lakes, ponds, streams, rivers, estuaries, and oceans.

Aquatic Microorganisms

Large numbers of microorganisms in a body of water generally indicate high nutrient levels in the water. Water contaminated by inflows from sewage systems or from biodegradable industrial organic wastes is relatively high in bacterial numbers. Similarly, ocean estuaries (fed by rivers) have higher nutrient levels and therefore larger microbial populations than other shoreline waters.

In water, particularly with low nutrient concentrations, microorganisms tend to grow on stationary surfaces and on particulate matter. In this way, a microorganism has contact with more nutrients than if it were randomly suspended and floating freely with the current. Many bacteria whose main habitat is water often have appendages and holdfasts that attach to various surfaces. One example is *Caulobacter* (see Figure 11.2, page 294).

Freshwater Microbiota

A typical lake or pond serves as an example of the various zones and the kinds of microbiota found in a body of fresh water. The **littoral zone** along the shore has considerable rooted vegetation, and light penetrates throughout it. The **limnetic zone** consists of the surface of the open water area away from the shore. The **profundal zone** is the deeper water under the limnetic zone. The **benthic zone** contains the sediment at the bottom.

Microbial populations of freshwater bodies tend to be affected mainly by the availability of oxygen and light. In many ways, light is the more important resource because photosynthetic algae are the main source of organic matter, and hence of energy, for the lake. These organisms are the primary producers of a lake that support a population of bacteria, protozoa, fish, and other aquatic life. Photosynthetic algae are located in the limnetic zone.

Oxygen does not diffuse into water very well, as any aquarium owner knows. Microorganisms growing on nutrients in stagnant water quickly use up the dissolved oxygen in the water. In the oxygenless water, fish die, and anaerobic activity produces odors. Wave action in shallow layers, or water movement in rivers, tends to increase the amount of oxygen throughout the water and aid in the growth of aerobic populations of bacteria. Movement thus improves the quality of water and aids in the degradation of polluting nutrients.

Deeper waters of the profundal and benthic zones have low oxygen concentrations and less light. Algal growth near the surface often filters the light, and it is not unusual for photosynthetic microbes in deeper zones to use different wavelengths of light from those used by surface-layer photosynthesizers (see Figure 12.12a, page 333).

Purple and green sulfur bacteria are found in the profundal zone. These bacteria are anaerobic photosynthetic organisms that metabolize H_2S to sulfur and sulfate in the bottom sediments of the benthic zone.

The sediment in the benthic zone includes bacteria such as *Desulfovibrio* that use sulfate (SO_4^{2-}) as an electron acceptor and reduce it to H_2S. Methane-producing bacteria are also part of these anaerobic benthic populations. In swamps, marshes, or bottom sediments, they produce methane gas. *Clostridium* species are common in bottom sediments and may include botulism organisms, particularly those causing outbreaks of botulism in waterfowl.

Seawater Microbiota

As knowledge of the microbial life of the oceans expands, largely identified by ribosomal RNA methods (see the discussion of FISH on page 283 in Chapter 10), biologists are becoming more conscious of the importance of oceanic microbes. Seafloor sediments have been found to have large populations of bacteria. These organisms are mostly Archaea, which adapt well to environmental stresses and have low energy requirements. One conclusion, so far, has been that nearly a third of all life on the planet consists of microbes that live, not in ocean waters, but under the seafloor. These microbes make immense amounts of methane gas that could be environmentally damaging if it were to be released into the atmosphere.

In the upper, relatively sunlit waters of the ocean, photosynthetic cyanobacteria of the genera *Synechococcus* (si-nek-ō-KOK-kus) and *Prochlorococcus* (prō-KLŌR-ō-kok-kus) are abundant. Populations of different strains vary at different depths according to their adaptations to available sunlight. A drop of seawater might contain 20,000 cells of *Prochlorococcus,* a tiny sphere less than 0.7 µm in diameter. This unseen population of microscopic organisms fills the upper 100 meters of ocean and exerts a profound influence on life on Earth. The support of oceanic life depends largely on



Figure 27.9 Bioluminescent bacteria as light organs in fish. This is a deep-sea flashlight fish (*Photoblepharon palpebratus*). The luminous organ under the eye can be covered by a tissue lid.

Q What enzyme is responsible for bioluminescence?

such photosynthetic microscopic life, the marine **phytoplankton** (a term derived from the Greek for wandering plants).

Photosynthetic bacteria such as these form the basis of the oceanic food chain. Billions of these in every liter of seawater double in number every few days and are consumed at about the same rate by microscopic predators. They fix carbon dioxide to form organic matter that is eventually released as dissolved organic matter and is used by the ocean's heterotrophic bacteria. A cyanobacterium, *Trichodesmium* (TRĪ-kō-des-mē-um), fixes nitrogen and helps replenish the nitrogen that is lost as organisms sink to oceanic depths. Immense populations of another bacterium, *Pelagibacter ubique,* metabolize the waste products of these photosynthetic populations (see the discussion under Microbial Diversity in Chapter 11 on page 315).

In waters below about 100 meters, members of the Archaea begin to dominate microbial life. Planktonic members of this group of the genus *Crenarchaeota* (kren-ar-KĒ-ō-tah) account for much of the microbial biomass of the oceans. These organisms are well adapted to the cool temperatures and low oxygen levels of oceanic depths. Their carbon is primarily derived from dissolved CO_2.

Microbial **bioluminescence,** or light emission, is an interesting aspect of deep-sea life. Many bacteria are luminescent, and some have established symbiotic relationships with benthic-dwelling fish. These fish sometimes use the glow of their resident bacteria as an aid in attracting and capturing prey in the complete darkness of the ocean depths (**Figure 27.9**). These bioluminescent organisms have an enzyme called *luciferase* that picks up electrons from flavoproteins in the electron transport chain and then emits some of the electron's energy as a photon of light (see the Applications of Microbiology box on page 783).

CHECK YOUR UNDERSTANDING

Purple and green sulfur bacteria are photosynthetic organisms, but they are generally found deep in freshwater rather than at the surface. Why? **27-13**

The Role of Microorganisms in Water Quality

Water in nature is seldom totally pure. Even rainfall is contaminated as it falls to Earth.

Water Pollution

The form of water pollution that is our primary interest is microbial pollution, especially by pathogenic organisms.

The Transmission of Infectious Diseases Water that moves below the ground's surface undergoes a filtering that removes most microorganisms. For this reason, water from springs and deep wells is generally of good quality. The most dangerous form of water pollution occurs when feces enter the water supply. Many diseases are perpetuated by the fecal–oral route of transmission, in which a pathogen is shed in human or animal feces, contaminates water, and is ingested (see Chapter 25). Globally, it is estimated that waterborne diseases are responsible for over 2 million deaths each year, mostly among children under the age of 5.

Examples of such diseases are typhoid fever and cholera, caused by bacteria that are shed only in human feces. Improvements in sanitation, including the use of sand filter beds, in developed nations have greatly reduced incidence.

Chemical Pollution Preventing chemical contamination of water is a difficult problem. Industrial and agricultural chemicals leached from the land enter water in great amounts and in forms that are resistant to biodegradation. Rural waters often have excessive amounts of nitrate from agricultural fertilizers. When ingested, the nitrate is converted to nitrite by bacteria in the gastrointestinal tract. Nitrite competes for oxygen in the blood and is especially likely to harm infants.

An example of chemical pollution is the synthetic detergents developed immediately after World War II. These rapidly replaced many of the soaps then in use. Because these new

Clinical Case

The physician prescribes a single dose of doxycycline and tells Charity to drink plenty of liquids. He also asks what countries Charity had visited. She tells him that she had been to China, the Philippines, Haiti, Chile, and Indonesia. Before she became ill, Charity had been in good health. Just before leaving Haiti to go home, Charity had eaten fried shrimp and prawns purchased from a local market and prepared by a local family. She also recalled drinking a half glass of water with her dinner; she did not know whether it was bottled water.

What should the physician suspect to be the cause of Charity's severe diarrhea ?



Figure 27.10 A red tide. These blooms of aquatic growth are caused by excess nutrients in water. The color is from the pigmentation of the dinoflagellates.

Q What is the primary energy source of the dinoflagellates that cause such aquatic blooms?

detergents were not biodegradable, they rapidly accumulated in the waterways. In some rivers, large rafts of detergent suds could be seen traveling downstream. These detergents were replaced by biodegradable synthetic formulations.

Biodegradable detergents, however, still present a major environmental problem because they often contain phosphates. Unfortunately, phosphates pass almost unchanged through sewage systems and can lead to **eutrophication,** which is caused by an overabundance of nutrients in lakes and streams.

To understand the concept of eutrophication, recall that algae and cyanobacteria get their energy from sunlight and their carbon from carbon dioxide dissolved in water. In most waters, only nitrogen and phosphorus supplies, therefore, remain inadequate for algal growth. Both of these nutrients can enter water from domestic, farm, and industrial wastes when waste treatment is absent or inefficient. These additional nutrients cause dense aquatic growths called **algal blooms.** Because many cyanobacteria can fix nitrogen from the atmosphere, these photosynthesizing organisms require only traces of phosphorus to initiate blooms. Once eutrophication results in blooms of algae or cyanobacteria, the eventual effect is the same as adding biodegradable organic matter. In the short run, these algae and cyanobacteria produce oxygen. However, they eventually die and are degraded by bacteria. During the degradation process, the oxygen in the water is used up, killing the fish. Undegraded remnants of organic matter settle to the bottom and hasten the filling of the lake.

Red tides of toxin-producing phytoplankton (**Figure 27.10**), which were mentioned in Chapter 12, are probably caused by excessive nutrients from oceanic upwellings or terrestrial wastes. In addition to eutrophication effects, this type of biological bloom can affect human health. Seafood, especially clams or similar mollusks, that ingest these plankton become toxic to humans.

Municipal waste containing detergents is likely to be the main source of phosphates in lakes and streams. As a result, phosphate-containing detergents and lawn fertilizers are banned in many places.

Water Purity Tests

Historically, most of our concern about water purity has been related to the transmission of disease. Therefore, tests have been developed to determine the safety of water; many of these tests are also applicable to foods.

It is not practical, however, to look only for pathogens in water supplies. For one thing, if we were to find the pathogens causing typhoid or cholera in the water system, the discovery would already be too late to prevent an outbreak of the disease. Moreover, such pathogens would probably be present only in small numbers and might not be included in tested samples.

The tests for water purity in use today are aimed instead at detecting particular **indicator organisms.** There are several criteria for an indicator organism. The most important criterion is that the microbe be consistently present in human feces in substantial numbers so that its detection is a good indication that human wastes are entering the water. The indicator organisms should also survive in the water at least as well as the pathogens would. The indicator organisms must be detectable by simple tests that can be carried out by people with relatively little training in microbiology.

In the United States, the usual indicator organisms in freshwater are the *coliform bacteria.** **Coliforms** are defined as aerobic or facultatively anaerobic, gram-negative, non–endospore-forming, rod-shaped bacteria that ferment lactose to form gas within 48 hours of being placed in lactose broth at 35°C. Because some coliforms are not solely enteric bacteria but are more commonly found in plant and soil samples, many standards for food and water specify the identification of *fecal coliforms.* The predominant fecal coliform is *E. coli,* which constitutes a large proportion of the human intestinal population. There are specialized tests to distinguish fecal coliforms from nonfecal coliforms. Note that coliforms are not themselves pathogenic under normal conditions, although certain strains can cause diarrhea (see Chapter 25, page 719) and opportunistic urinary tract infections (see Chapter 26, page 749).

The methods for determining the presence of coliforms in water are based largely on the lactose-fermenting ability of coliform bacteria. The multiple-tube method can be used to estimate coliform numbers by the most probable number (MPN) method (see Figure 6.19, page 170). The membrane filtration method is a more direct method of determining the presence and numbers of coliforms. This is possibly the most widely used

*The U.S. Environmental Protection Agency (EPA) recommends the use of *Enterococcus* bacteria as a safety indicator for waters in oceans and bays. Populations of the enterococci decrease more uniformly than coliforms in both freshwater and seawater.

Biosensors: Bacteria That Detect Pollutants and Pathogens

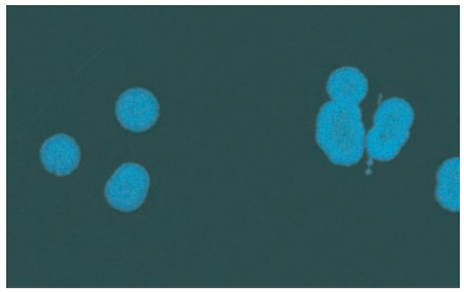
Each year in the United States, industrial plants generate 265 million metric tons of hazardous waste, 80% of which makes its way into landfills. Burying these chemicals does not remove them from the ecosystem, however; they may still find their way into bodies of water. Traditional chemical analyses to locate these chemicals are expensive and cannot distinguish chemicals that affect biological systems from those that lie inert.

In response to this problem, scientists are developing biosensors, bacteria that can locate biologically active pollutants. Biosensors do not require costly chemicals or equipment, and they work quickly—within minutes.

To work, bacterial biosensors require both a receptor that is activated in the presence of pollutants and a reporter that records changes. Biosensors use the *lux* operon from *Aliivibrio* or *Photobacterium* as a reporter. This operon contains inducer and structural genes for the enzyme luciferase. In the presence of a coenzyme called $FMNH_2$, luciferase reacts with the molecule in such a way that the enzyme–substrate complex emits blue-green light, which then oxidizes the $FMNH_2$ to produce FMN. A bacterium containing the *lux* operon will emit visible light when the receptor is activated (see the photograph).

The *lux* operon is readily transferred to many bacteria. Scientists in several countries are investigating the use of *E. coli* containing the *lux* operon to detect hazardous chemicals in soil and water. The soil or water sample is placed in a tube containing the genetically modified *E. coli* bacteria. The bacteria will emit light as long as they are healthy but will stop emitting light when killed by toxic pollutants.

In another application, *Lactococcus* bacteria containing the *lux* operon can detect the presence of antibiotics in milk to be used for cheese production. Because light emission requires a living cell, the presence of antibiotics is measured as a decrease in light output.



***Aliivibrio fischeri* emits light when energy is released by the transport of electrons to luciferase. Shown here are colonies of *A. fischeri* photographed in the dark, illuminated by their own light.**

Other biosensors use recombinant microbes carrying a jellyfish gene for green fluorescent protein (GFP) and genes that are induced by pollutants or antibiotics. For example, yeast containing genes encoding mammalian odor receptors and GFP will fluoresce in the presence of TNT-containing explosives.

method in North America and Europe. It makes use of a filtration apparatus similar to that shown in Figure 7.4 (page 183). In this application, though, the bacteria collected on the surface of a removable membrane filter are placed on an appropriate medium and incubated. Coliform colonies have a distinctive appearance and are counted. This method is suitable for low-turbidity waters that do not clog the filter and have relatively few noncoliform bacteria that would mask the results.

A newer and more convenient method of detecting coliforms, specifically the fecal coliform *E. coli,* makes use of media containing the two substrates *o*-nitrophenyl-β-D-galactopyranoside (ONPG) and 4-methylumbelliferyl-β-D-glucuronide (MUG). Coliforms produce the enzyme β-galactosidase, which acts on ONPG and forms a yellow color, indicating their presence in the sample. *E. coli* is unique among coliforms in almost always producing the enzyme β-glucuronidase, which acts on MUG to form a fluorescent compound that glows blue when illuminated by long-wave UV light. It can also be applied to solid media, such as in the membrane filtration method. The colonies fluoresce under UV light. These simple tests, or variants of them, can detect the presence or absence of coliforms or *E. coli* and can be combined with the multiple-tube method to enumerate them.

Coliforms have been very useful as indicator organisms in water sanitation, but they have limitations. One problem is the growth of coliform bacteria embedded in biofilms on the inner surfaces of water pipes. These coliforms do not, then, represent external fecal contamination of the water, and they are not considered a threat to public health. Standards governing the presence of coliforms in drinking water require that any positive water sample be reported, and occasionally these indigenous coliforms have been detected. This has led to unnecessary community orders to boil water.

A more serious problem is that some pathogens, especially viruses and protozoan cysts and oocysts, are more resistant than coliforms to chemical disinfection. Through the use of sophisticated

Clinical Case

The physician suspects cholera, and he sends a stool sample to a local laboratory. The stool culture yields colonies suspected of being *Vibrio cholerae.* This result is confirmed by the county public health laboratory. Latex agglutination tests in the state public health laboratory confirm that the colonies are producing cholera toxin. Further testing at the CDC identifies the isolate as the El Tor biotype of *V. cholerae* O:1. DNA fingerprinting shows that this is the same strain of *V. cholerae* that is causing an epidemic in Haiti.

How is cholera transmitted? How does an earthquake promote transmission?

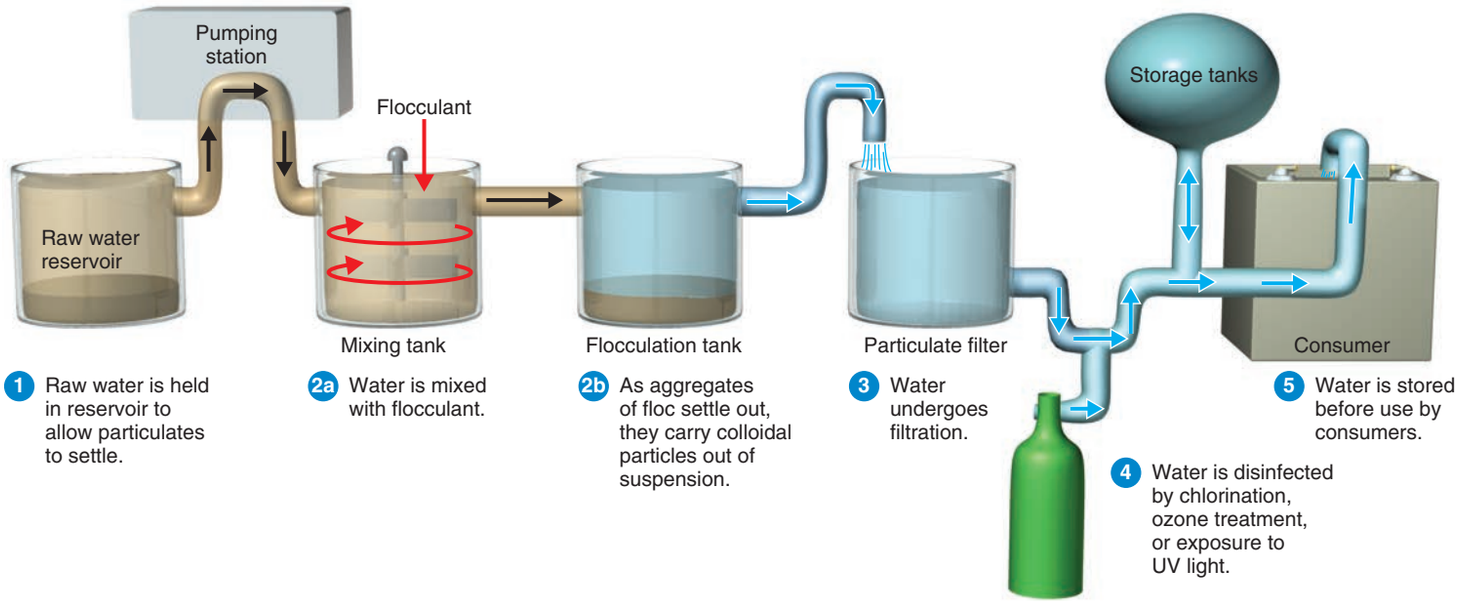


Figure 27.11 The steps involved in water treatment in a typical municipal water purification plant.

Q Does removal of "colloidal particles" by flocculation involve living organisms?

methods of detecting viruses, it has been found that chemically disinfected water samples that are free of coliforms are often still contaminated with enteric viruses. The cysts of *Giardia intestinalis* and oocysts of *Cryptosporidium* are so resistant to chlorination that completely eliminating them by this method is probably impractical; mechanical methods such as filtration are necessary. A general rule for chlorination is that viruses are more resistant to treatment than is *E. coli* and that the cysts of *Cryptosporidium* and *Giardia* are 100 times more resistant than viruses.

CHECK YOUR UNDERSTANDING

- Which disease is more likely to be transmitted by polluted water, cholera or influenza? **27-14**
- Name a microorganism that will grow in water even if there is no source of organic matter for energy or a nitrogen source—but does require small inputs of phosphorus. **27-15**
- Coliforms are the most common bacterial indicator of health-threatening water pollution in the United States. Why is it usually necessary to specify the term *fecal* coliform? **27-16**

Water Treatment

When water is obtained from uncontaminated reservoirs fed by clear mountain streams or from deep wells, it requires minimal treatment to make it safe to drink. Many cities, however, obtain their water from badly polluted sources, such as rivers that have received municipal and industrial wastes upstream. The steps used to purify this water are shown in **Figure 27.11**. Water treatment is not intended to produce sterile water, but rather water that is free of disease-causing microbes.

Coagulation and Filtration

Very turbid (cloudy) water is allowed to stand in a holding reservoir for a time to allow as much particulate suspended matter as possible to settle out. The water then undergoes **flocculation,** the removal of colloidal materials such as clay, which is so small (smaller than 10 μm) that it would otherwise remain in suspension indefinitely. A flocculant chemical, such as aluminum potassium sulfate (alum), forms aggregations of fine suspended particles called *floc.* As these aggregations slowly settle out, they entrap colloidal material and carry it to the bottom. Large numbers of viruses and bacteria are also removed this way. Alum was used to clear muddy river water during the first half of the nineteenth century in the military forts of the American West, long before the germ theory of disease was developed.

After flocculation, the water is treated by **filtration**—that is, passing it through beds of 2 to 4 feet of fine sand or crushed anthracite coal. As mentioned previously, some protozoan cysts and oocysts are removed from water only by such filtration treatment. The microorganisms are trapped mostly by surface adsorption onto the sand particles. They do not penetrate the tortuous routing between the particles, even though the openings might be larger than the microbes that are filtered out. These filters are periodically backflushed to clear them of accumulations. Water systems of cities that have an exceptional concern for toxic chemicals supplement sand filtration with filters of activated charcoal (carbon). Charcoal removes not only particulate matter but also most dissolved organic chemical pollutants. A properly operated water treatment plant

will remove viruses (which are harder to remove than bacteria and protozoa) with an efficiency of about 99.5%. Low-pressure *membrane filtration systems* are now coming into use. These systems have pore openings as small as 0.2 µm and are more reliable for removal of *Giardia* and *Cryptosporidium.*

Disinfection

Before entering the municipal distribution system, the filtered water is chlorinated. Because organic matter neutralizes chlorine, the plant operators must pay constant attention to maintaining effective levels of chlorine.

As noted in Chapter 7 (page 194), another disinfectant for water is ozone treatment. Ozone (O_3) is a highly reactive form of oxygen that is formed by electrical spark discharges and UV light. (The fresh odor of air following an electrical storm or around a UV light bulb is from ozone.) Ozone for water treatment is generated electrically at the site of treatment. Ozone treatment is also valued because it leaves no taste or odor. Because it has little residual effect, ozone is usually used as a primary disinfectant treatment and is followed by chlorination. The use of UV light is also a supplement or alternative to chemical disinfection. Ultraviolet tube lamps are arranged so that water flows close to them. This is necessary because of the low penetrating power of UV radiation.

CHECK YOUR UNDERSTANDING

How do flocculants such as alum remove colloidal impurities, including microorganisms, from water? **27-17**

Sewage (Wastewater) Treatment

Sewage, or wastewater, includes all the water from a household that is used for washing and toilet wastes. Rainwater flowing into street drains and some industrial wastes enter the sewage system in many cities. Sewage is mostly water and contains little particulate matter, perhaps only 0.03%. Even so, in large cities the solid portion of sewage can total more than 1000 tons of solid material per day.

Until environmental awareness intensified, a surprising number of large American cities had only a rudimentary sewage treatment system or no system at all. Raw sewage, untreated or nearly so, was simply discharged into rivers or oceans. A flowing, well-aerated stream is capable of considerable self-purification. Therefore, until expanding populations and their wastes exceeded this capability, this casual treatment of municipal wastes did not cause problems. In the United States, most cases of simple discharge have been improved. But this is not true in much of the world. Many of the communities bordering the Mediterranean dump their unprocessed sewage into the sea.

Primary Sewage Treatment

The usual first step in sewage treatment is called **primary sewage treatment** (Figure 27.12a). In this process, large floating materials in incoming wastewater are screened out, the sewage is allowed to flow through settling chambers to remove sand and similar gritty material, skimmers remove floating oil and grease, and floating debris is shredded and ground. After this step, the sewage passes through sedimentation tanks, where more solid matter settles out. Sewage solids collecting on the bottom are called **sludge**—at this stage, *primary sludge.* About 40–60% of suspended solids are removed from sewage by this settling treatment, and flocculating chemicals that increase the removal of solids are sometimes added at this stage. Biological activity is not particularly important in primary treatment, although some digestion of sludge and dissolved organic matter can occur during long holding times. The sludge is removed on either a continuous or an intermittent basis, and the effluent (the liquid flowing out) then undergoes secondary treatment.

Biochemical Oxygen Demand

An important concept in sewage treatment and in the general ecology of waste management is **biochemical oxygen demand (BOD),** a measure of the biologically degradable organic matter in water. Primary treatment removes about 25–35% of the BOD of sewage.

BOD is determined by the amount of oxygen required by bacteria to metabolize the organic matter. The classic method of measurement is the use of special bottles with airtight stoppers. Each bottle is first filled with test water or dilutions. The water is initially aerated to provide a relatively high level of dissolved oxygen and is seeded with bacteria if necessary. The filled bottles are incubated in the dark for 5 days at 20°C, and the decrease in dissolved oxygen is determined by a chemical or electronic testing method. The more oxygen that is used up as the bacteria degrade the organic matter in the sample, the greater the BOD, which is usually expressed in milligrams of oxygen per liter of water. The amount of oxygen that normally can be dissolved in water is only about 10 mg/liter; typical BOD values of wastewater may be 20 times this amount. If this wastewater enters a lake, for example, bacteria in the lake begin to consume the organic matter responsible for the high BOD, rapidly depleting the oxygen in the lake water. (See the discussion of eutrophication on page 782.)

Secondary Sewage Treatment

After primary treatment, the greater part of the BOD remaining in the sewage is in the form of dissolved organic matter. **Secondary sewage treatment,** which is predominantly biological, is designed to remove most of this organic matter and reduce the BOD (Figure 27.12b). In this process, the sewage undergoes strong aeration to encourage the growth of aerobic bacteria and other microorganisms that oxidize the dissolved organic matter to carbon dioxide and water. Two commonly used methods of secondary treatment are activated sludge systems and trickling filters.

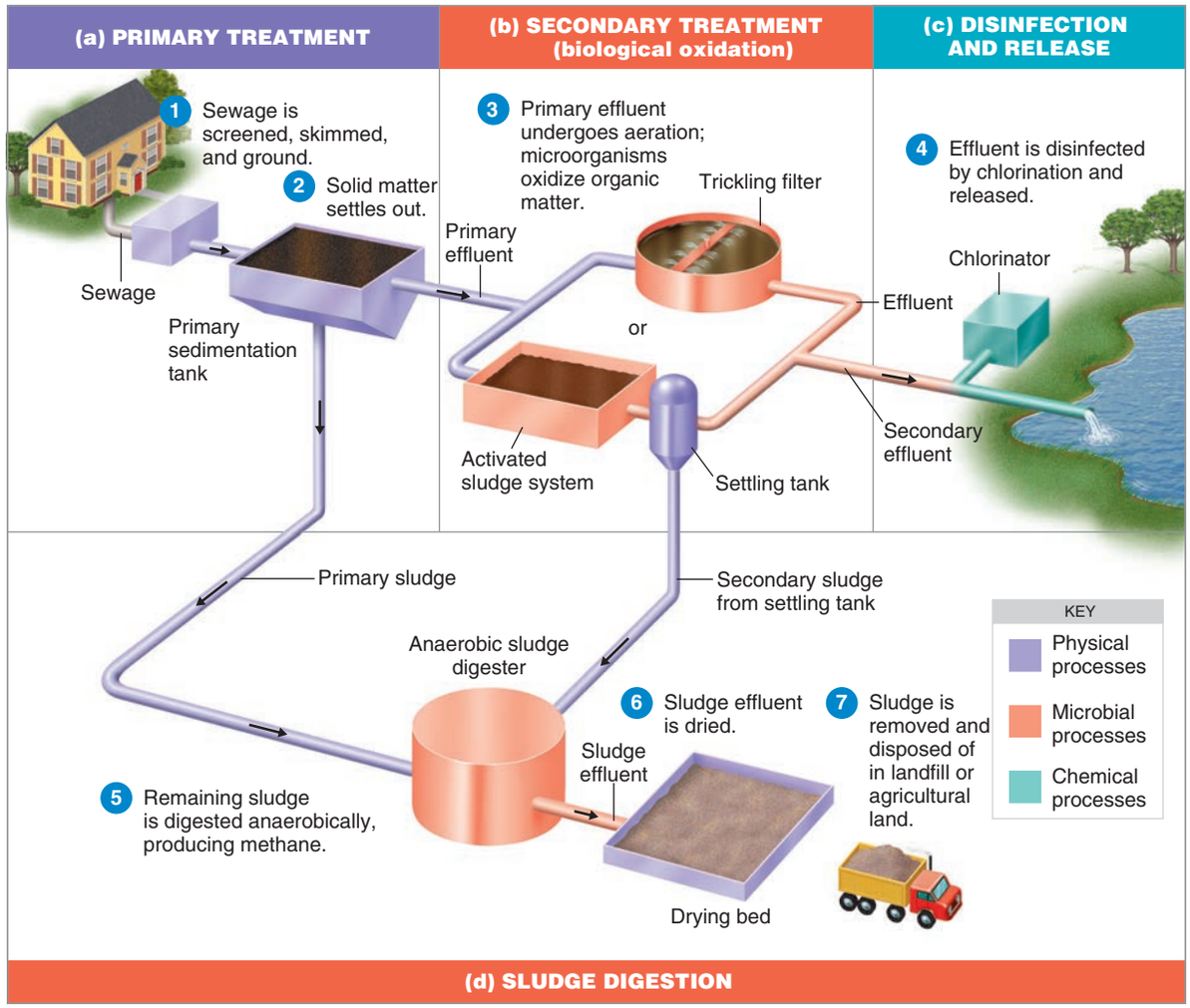


Figure 27.12 The stages in typical sewage treatment. Microbial activity occurs aerobically in trickling filters or activated sludge aeration tanks and anaerobically in the anaerobic sludge digester. A particular system would use either activated sludge aeration tanks or trickling filters, not both, as shown in this figure. Methane produced by sludge digestion is burned off or used to power heaters or pump motors.

Q Which processes require oxygen?

In the aeration tanks of an **activated sludge system,** air or pure oxygen is passed through the effluent from primary treatment (Figure 27.13). The name is derived from the practice of adding some of the sludge from a previous batch to the incoming sewage. This inoculum is termed *activated sludge* because it contains large numbers of sewage-metabolizing microbes. The activity of these aerobic microorganisms oxidizes much of the sewage organic matter into carbon dioxide and water. Especially important members of this microbial community are species of *Zoogloea* bacteria, which form bacteria-containing masses in the aeration tanks called floc, or *sludge granules*. Soluble organic matter in the sewage is incorporated into the floc and its microorganisms. Aeration is discontinued after 4 to 8 hours, and the contents of the tank are transferred to a settling tank, where the floc settles out, removing much of the organic matter. These solids are subsequently treated in an anaerobic sludge digester, which will be described shortly. Probably more organic matter is removed by this settling-out process than by the relatively short-term aerobic oxidation by microbes. The clear effluent is disinfected and discharged.

Occasionally, the sludge will float rather than settle out; this phenomenon is called **bulking.** When this happens, the organic matter in the floc flows out with the discharge effluent, resulting in local pollution. Bulking is caused by the growth of filamentous bacteria of various types; *Sphaerotilus natans* and *Nocardia* species are frequent offenders. Activated sludge systems are quite efficient: they remove 75–95% of the BOD from sewage.

Trickling filters are the other commonly used method of secondary treatment. In this method, the sewage is sprayed over a bed of rocks or molded plastic (Figure 27.14). The components of the

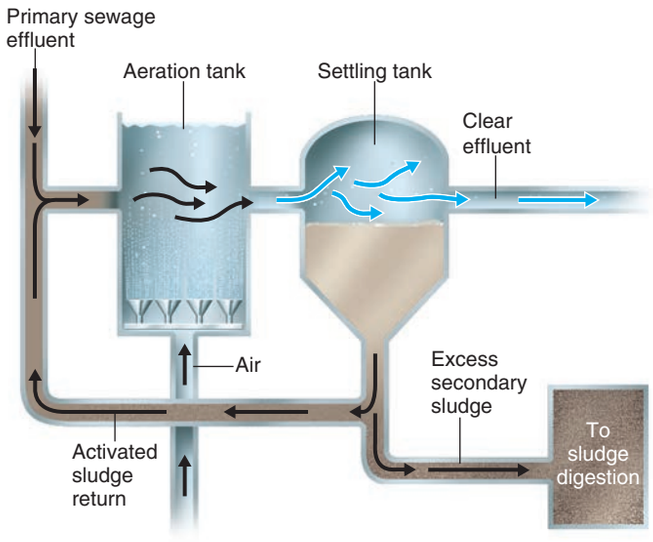


Figure 27.13 An activated sludge system of secondary sewage treatment.

Q What are the similarities between winemaking and activated sludge sewage treatment?

bed must be large enough so that air penetrates to the bottom but small enough to maximize the surface area available for microbial activity. A biofilm (see page 156) of aerobic microbes grows on the rock or plastic surfaces. Because air circulates throughout the rock bed, these aerobic microorganisms in the slime layer can oxidize much of the organic matter trickling over the surfaces into carbon dioxide and water. Trickling filters remove 80–85% of the BOD, so they are generally less efficient than activated sludge systems.

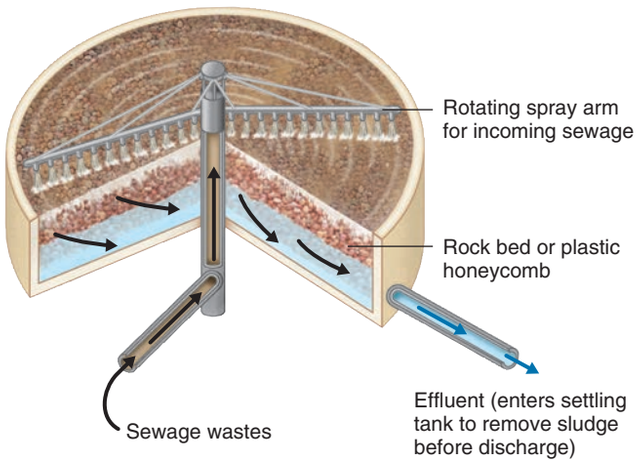


Figure 27.14 A trickling filter of secondary sewage treatment. The sewage is sprayed from the system of rotating pipes onto a bed of rocks or plastic honeycomb designed to have a maximum surface area and to allow oxygen to penetrate deeply into the bed.

Q Which would make the more efficient bed for a trickling filter system, fine sand or golf balls?

However, they are usually less troublesome to operate and have fewer problems from overloads or toxic sewage. Note that sludge is also a product of trickling filter systems.

Another biofilm-based design for secondary sewage treatment is the **rotating biological contactor** system. This is a series of disks several feet in diameter, mounted on a shaft. The disks rotate slowly, with their lower 40% submerged in wastewater. Rotation provides aeration and contact between the biofilm on the disks and the wastewater. The rotation also tends to cause the accumulated biofilm to slough off when it becomes too thick. This is about the equivalent of floc accumulation in activated sludge systems.

Disinfection and Release

Treated sewage is disinfected, usually by chlorination, before being discharged (Figure 27.12c). The discharge is usually into an ocean or into flowing streams, although spray-irrigation fields are sometimes used to avoid phosphorus and heavy metal contamination of waterways.

Sewage can be treated to a level of purity that allows its use as drinking water—winningly termed "toilet to tap." This is the practice now in some arid-area cities in the United States and may be expanded. In a typical system, the treated sewage is filtered to remove microscopic suspended particles, then passed through a reverse osmosis purification system to remove microorganisms. Any remaining microorganisms are killed by exposure to UV light and hydrogen peroxide.

Sludge Digestion

Primary sludge accumulates in primary sedimentation tanks; sludge also accumulates in activated sludge and in trickling filter secondary treatments. For further treatment, these sludges are often pumped to **anaerobic sludge digesters** (Figure 27.12d

Clinical Case

V. cholerae is transmitted by the fecal–oral route. Prior to the earthquake, only 63% of Haiti's population had access to an improved drinking water source (a closed well, chlorine, or filtration and safe storage containers), and only 17% had access to adequate sanitation. Many people used springs for their drinking water. Cholera spread rapidly across Haiti 9 months after the earthquake because of the lack of safe water and sanitation and the large numbers of displaced people. The fatality rate from cholera in Haiti is 3.3%.

Charity recovers uneventfully; why is the case fatality rate so high in Haiti?

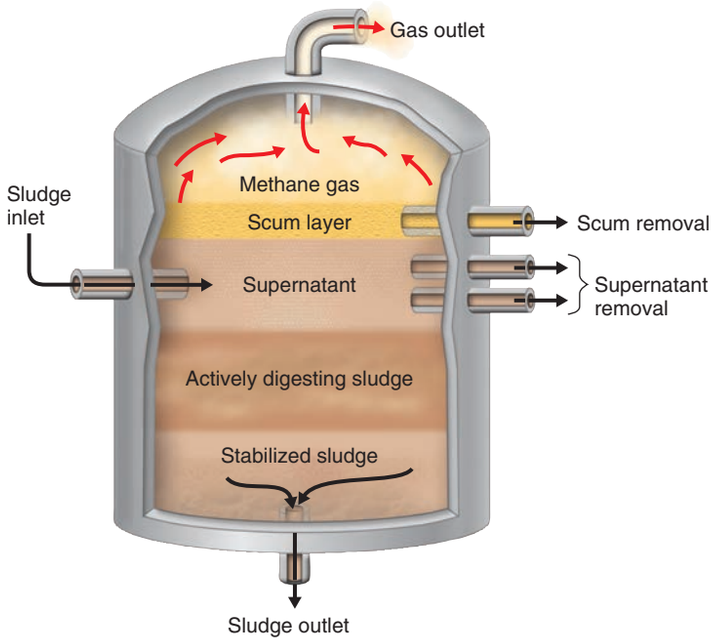


Figure 27.15 Sludge digestion.

Q What might be some uses for the stabilized sludge?

and Figure 27.15). The process of sludge digestion is carried out in large tanks from which oxygen is almost completely excluded.

In secondary treatment, emphasis is placed on maintaining aerobic conditions so that organic matter is converted to carbon dioxide, water, and solids that can settle out. An anaerobic sludge digester, however, is designed to encourage the growth of anaerobic bacteria, especially methane-producing bacteria that decrease these organic solids by degrading them to soluble substances and gases, mostly methane (60–70%) and carbon dioxide (20–30%). Methane and carbon dioxide are relatively innocuous end-products, comparable to the carbon dioxide and water from aerobic treatment. The methane is routinely used as a fuel for heating the digester and is also frequently used to run power equipment in the plant.

There are essentially three stages in the activity of an anaerobic sludge digester. The first stage is the production of carbon dioxide and organic acids from anaerobic fermentation of the sludge by various anaerobic and facultatively anaerobic microorganisms. In the second stage, the organic acids are metabolized to form hydrogen and carbon dioxide, as well as organic acids such as acetic acid. These products are the raw materials for a third stage, in which the methane-producing bacteria produce methane (CH_4). Most of the methane is derived from the energy-yielding reduction of carbon dioxide by hydrogen gas:

$$CO_2 + 4H_2 \longrightarrow CH_4 + 2H_2O$$

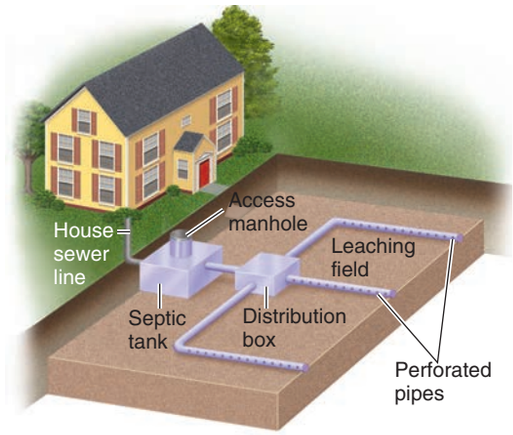
Other methane-producing microbes split acetic acid (CH_3COOH) to yield methane and carbon dioxide:

$$CH_3COOH \longrightarrow CH_4 + CO_2$$

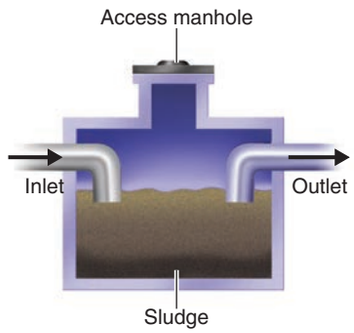
After anaerobic digestion is completed, large amounts of undigested sludge still remain, although it is relatively stable and inert. To reduce its volume, this sludge is pumped to shallow drying beds or water-extracting filters. Following this step, the sludge can be used for landfill or as a soil conditioner, sometimes under the name *biosolids*. Sludge is assigned to two classes: class A sludge contains no detectable pathogens, and class B sludge is treated only to reduce numbers of pathogens below certain levels. Most sludge is class B, and public access to application sites is limited. Sludge has about one-fifth the growth-enhancing value of normal commercial lawn fertilizers but has desirable soil-conditioning qualities, much as do humus and mulch. A potential problem is contamination with heavy metals that are toxic to plants.

Septic Tanks

Homes and businesses in areas of low population density that are not connected to municipal sewage systems often use a **septic tank,** a device whose operation is similar in principle to primary treatment (Figure 27.16). Sewage enters a holding



(a) Overall plan. Most soluble organic matter is disposed of by percolation into the soil.



(b) A section of a septic tank

Figure 27.16 A septic tank system.

Q Which type of soil would require the larger drainage area, clay or sandy?

Clinical Case

When cholera is recognized early and appropriate rehydration treatment (see pages 717–718) is initiated rapidly, the fatality rate is less than 1%. The underlying poor nutritional status of the people affected and lack of safe water for rehydration therapy contributes to the high mortality rate. Moreover, epidemic cholera has not been reported previously from Haiti; consequently, the population is immunologically naïve and therefore highly susceptible to infection with *V. cholerae*.

Using these data from Haiti, what would you recommend?

Types of Water	Coliforms per 100 ml
Raw (untreated) water	323
Water treated with chlorine (2 drops of household bleach/liter; wait 30 min)	0
Water treated with ceramic filtration	0

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tank, and suspended solids settle out. The sludge in the tank must be pumped out periodically and disposed of. The effluent flows through a system of perforated piping into a leaching (soil drainage) field. The effluent entering the soil is decomposed by soil microorganisms. The microbial action necessary for proper functioning of a septic tank can be impaired by excessive amounts of products such as antibacterial soaps, drain cleaners, medications, "every flush" toilet bowl cleaners, and bleach.

These systems work well when not overloaded and when the drainage system is properly sized to the load and soil type. Heavy clay soils require extensive drainage systems because of the soil's poor permeability. The high porosity of sandy soils can result in chemical or bacterial pollution of nearby water supplies.

Oxidation Ponds

Many industries and small communities use **oxidation ponds,** also called *lagoons* or *stabilization ponds,* for water treatment. These are inexpensive to build and operate but require large areas of land. Designs vary, but most incorporate two stages. The first stage is analogous to primary treatment; the sewage pond is deep enough that conditions are almost entirely anaerobic. Sludge settles out in this stage. In the second stage, which roughly corresponds to secondary treatment, effluent is pumped into an adjoining pond or system of ponds shallow enough to be aerated by wave action. Because it is difficult to maintain aerobic conditions for bacterial growth in ponds with so much organic matter, the growth of algae is encouraged to produce oxygen. Bacterial action in decomposing the organic matter in the wastes generates carbon dioxide. Algae, which use carbon dioxide in their photosynthetic metabolism, grow and produce oxygen, which in turn encourages the activity of aerobic microbes in the sewage. Large amounts of organic matter in the form of algae accumulate, but this is not a problem because the oxidation pond, unlike a lake, already has a large nutrient load.

Some small sewage-producing operations, such as isolated campgrounds and highway rest stop areas, use an *oxidation ditch* for sewage treatment. In this method, a small oval channel in the shape of a racetrack is filled with sewage water. A paddle wheel propels the water in a self-contained flowing stream aerated enough to oxidize the wastes.

Tertiary Sewage Treatment

As we have seen, primary and secondary treatments of sewage do not remove all the biologically degradable organic matter. Amounts of organic matter that are not excessive can be released into a flowing stream without causing a serious problem. Eventually, however, the pressures of increased population might increase wastes beyond a body of water's carrying capacity, and additional treatments might be required. Even now, primary and secondary treatments are inadequate in certain situations, such as when the effluent is discharged into small streams or recreational lakes. Some communities have therefore developed **tertiary sewage treatment** plants. Lake Tahoe in the Sierra Nevada, surrounded by extensive development, is the site of one of the best-known tertiary sewage treatment systems. Similar systems are used to treat wastes entering the southern portion of San Francisco Bay.

The effluent from secondary treatment plants contains some residual BOD. It also contains about 50% of the original nitrogen and 70% of the original phosphorus, which can greatly affect a lake's ecosystem. Tertiary treatment is designed to remove essentially all the BOD, nitrogen, and phosphorus. Tertiary treatment depends less on biological treatment than on physical and chemical treatments. Phosphorus is precipitated out by combining with such chemicals as lime, alum, and ferric chloride. Filters of fine sands and activated charcoal remove small particulate matter and dissolved chemicals. Nitrogen is converted to ammonia and discharged into the air in stripping towers. Some systems encourage denitrifying bacteria to form volatile nitrogen gas. Finally, the purified water is chlorinated.

Tertiary treatment provides water that is suitable for drinking, but the process is extremely costly. Secondary treatment is less costly, but water that has undergone only secondary treatment still contains many water pollutants. Much work is being done to design secondary treatment plants in which the effluent can be used for irrigation. This design would eliminate a source

of water pollution, provide nutrients for plant growth, and reduce the demand on already scarce water supplies. The soil to which this water is applied would act as a trickling filter to remove chemicals and microorganisms before the water reaches groundwater and surface water supplies.

CHECK YOUR UNDERSTANDING

- Which type of sewage treatment is designed to remove almost all phosphorus from sewage? **27-18**
- What metabolic group of anaerobic bacteria is especially encouraged by operation of a sludge digestion system? **27-19**
- What is the relationship between BOD and the welfare of fish? **27-20**

Clinical Case Resolved

Improvements in water quality and sanitation are necessary to reduce transmission of cholera. Because cholera can progress quickly to severe dehydration, shock, and death, rapid rehydration is the mainstay of cholera treatment. However, rehydration therapy requires clean water, and water treatment must be inexpensive.

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Study Outline

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Microbial Diversity and Habitats (p. 772)

1. Microorganisms live in a wide variety of habitats because of their metabolic diversity and their ability to use a variety of carbon and energy sources and to grow under different physical conditions.
2. Extremophiles live in extreme conditions of temperature, acidity, alkalinity, or salinity.

Symbiosis (p. 772)

3. Symbiosis is a relationship between two different organisms or populations.
4. Symbiotic fungi called mycorrhizae live in and on plant roots; they increase the surface area and nutrient absorption of the plant.

Soil Microbiology and Biogeochemical Cycles (pp. 772–779)

1. In biogeochemical cycles, certain chemical elements are recycled.
2. Microorganisms in the soil decompose organic matter and transform carbon-, nitrogen-, and sulfur-containing compounds into usable forms.
3. Microbes are essential to the continuation of biogeochemical cycles.
4. Elements are oxidized and reduced by microorganisms during these cycles.

The Carbon Cycle (p. 773)

5. Carbon dioxide is incorporated, or fixed, into organic compounds by photoautotrophs and chemoautotrophs.
6. These organic compounds provide nutrients for chemoheterotrophs.
7. Chemoheterotrophs release CO_2 that is then used by photoautotrophs.
8. Carbon is removed from the cycle when it is in $CaCO_3$ and fossil fuels.

The Nitrogen Cycle (pp. 774–776)

9. Microorganisms decompose proteins from dead cells and release amino acids.
10. Ammonia is liberated by microbial ammonification of the amino acids.
11. The nitrogen in ammonia is oxidized to produce nitrates for energy by nitrifying bacteria.
12. Denitrifying bacteria reduce the nitrogen in nitrates to molecular nitrogen (N_2).
13. N_2 is converted into ammonia by nitrogen-fixing bacteria including free-living genera such as *Azotobacter* and cyanobacteria, and the symbiotic bacteria *Rhizobium* and *Frankia*.
14. Ammonium and nitrate are used by bacteria and plants to synthesize amino acids that are assembled into proteins.

The Sulfur Cycle (p. 776)

15. Hydrogen sulfide (H_2S) is used by autotrophic bacteria; the sulfur is oxidized to form S^0 or SO_4^{2-}.
16. Plants and other microorganisms can reduce SO_4^{2-} to make certain amino acids. These amino acids are in turn used by animals.
17. H_2S is released by decay or dissimilation of these amino acids.

Life without Sunshine (pp. 776–778)

18. Chemoautotrophs are the primary producers in deep-sea vents and within deep rocks.

The Phosphorus Cycle (p. 778)

19. Phosphorus (as PO_4^{3-}) is found in rocks and bird guano.
20. When solubilized by microbial acids, the PO_4^{3-} is available for plants and microorganisms.

The Degradation of Synthetic Chemicals in Soil and Water (pp. 778–779)

21. Many synthetic chemicals, such as pesticides, are resistant to degradation by microbes.
22. The use of microorganisms to remove pollutants is called bioremediation.
23. Municipal landfills prevent decomposition of solid wastes because they are dry and anaerobic.
24. In some landfills, methane produced by methanogens can be recovered for an energy source.

Aquatic Microbiology and Sewage Treatment (pp. 780–790)

Aquatic Microorganisms (pp. 780–781)

1. The study of microorganisms and their activities in natural waters is called aquatic microbiology.
2. Natural waters include lakes, ponds, streams, rivers, estuaries, and the oceans.
3. The concentration of bacteria in water is proportional to the amount of organic material in the water.
4. Most aquatic bacteria tend to grow on surfaces rather than in a free-floating state.
5. The number and location of freshwater microbiota depend on the availability of oxygen and light.
6. Photosynthetic algae are the primary producers of a lake; they are found in the limnetic zone.
7. Pseudomonads, *Cytophaga, Caulobacter,* and *Hyphomicrobium* are found in the limnetic zone, where oxygen is abundant.
8. Microbes in stagnant water use available oxygen and can cause odors and the death of fish.
9. Purple and green sulfur bacteria are found in the profundal zone, which contains light and H_2S but no oxygen.
10. *Desulfovibrio* reduces SO_4^{2-} to H_2S in benthic mud.
11. Methane-producing bacteria are also found in the benthic zone.
12. Phytoplankton are the primary producers of the open ocean.
13. *Pelagibacter ubique* is a decomposer in ocean waters.
14. Archaea predominate below 100 m.
15. Some algae and bacteria are bioluminescent. They possess the enzyme luciferase, which can emit light.

The Role of Microorganisms in Water Quality (pp. 781–784)

16. Microorganisms are filtered from water that percolates into groundwater supplies.
17. Some pathogenic microorganisms are transmitted to humans in drinking and recreational waters.
18. Resistant chemical pollutants may be concentrated in animals in an aquatic food chain.
19. Nutrients such as phosphates cause algal blooms, which can lead to eutrophication of aquatic ecosystems.
20. Tests for the bacteriological quality of water are based on the presence of indicator organisms, the most common of which are coliforms.
21. Coliforms are aerobic or facultatively anaerobic, gram-negative, non–endospore-forming rods that ferment lactose with the production of acid and gas within 48 hours of being placed in a medium at 35°C.
22. Fecal coliforms, predominantly *E. coli,* are used to indicate the presence of human feces.

Water Treatment (pp. 784–785)

23. Drinking water is held in a holding reservoir long enough that suspended matter settles.
24. Flocculation treatment uses a chemical such as alum to coalesce and then settle colloidal material.
25. Filtration removes protozoan cysts and other microorganisms.
26. Drinking water is disinfected with chlorine to kill remaining pathogenic bacteria.

Sewage (Wastewater) Treatment (pp. 785–790)

27. Domestic wastewater is called sewage; it includes household water, toilet wastes, and rainwater.
28. Primary sewage treatment is the removal of solid matter called sludge.
29. Biological activity is not very important in primary treatment.
30. Biochemical oxygen demand (BOD) is a measure of the biologically degradable organic matter in water.
31. Primary treatment removes about 25–35% of the BOD of sewage.
32. BOD is determined by measuring the amount of oxygen bacteria require to degrade the organic matter.
33. Secondary sewage treatment is the biological degradation of organic matter after primary treatment.
34. Activated sludge systems, trickling filters, and rotating biological contactors are methods of secondary treatment.
35. Microorganisms degrade the organic matter aerobically.
36. Secondary treatment removes up to 95% of the BOD.
37. Treated sewage is disinfected, usually by chlorination, before discharge onto land or into water.
38. Sludge is placed in an anaerobic sludge digester; bacteria degrade organic matter and produce simpler organic compounds, methane, and CO_2.
39. The methane produced in the digester is used to heat the digester and operate other equipment.
40. Excess sludge is periodically removed from the digester, dried, and disposed of (as landfill or soil conditioner) or incinerated.
41. Septic tanks can be used in rural areas to provide primary treatment of sewage.
42. Small communities can use oxidation ponds for secondary treatment.
43. These require a large area in which to build an artificial lake.
44. Tertiary sewage treatment uses physical filtration and chemical precipitation to remove all the BOD, nitrogen, and phosphorus from water.
45. Tertiary treatment provides drinkable water, whereas secondary treatment provides water usable only for irrigation.

Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

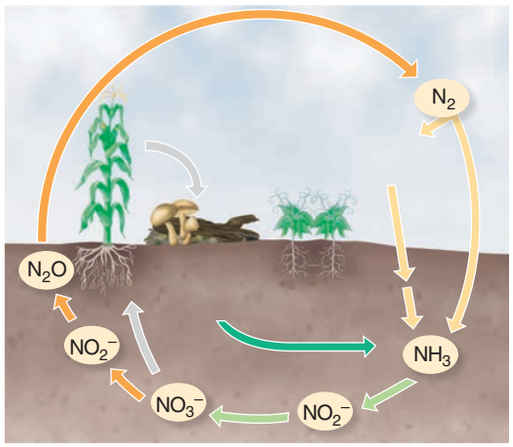
Knowledge and Comprehension

Review

1. The koala is a leaf-eating animal. What can you infer about its digestive system?
2. Give one possible explanation of why *Penicillium* would make penicillin, given that the fungus does not get bacterial infections.
3. In the sulfur cycle, microbes degrade organic sulfur compounds, such as (a)_____, to release H_2S, which can be oxidized by *Acidithiobacillus* to (b)_____. This ion can be assimilated into amino acids by (c)_____ or reduced by *Desulfovibrio* to (d)_____. H_2S is used by photoautotrophic bacteria

as an electron donor to synthesize (e)_____. The sulfur-containing by-product of this metabolism is (f)_____.

4. Why is the phosphorus cycle important?
5. DRAW IT Identify where the following processes occur: ammonification, decomposition, denitrification, nitrification, nitrogen fixation. Name at least one organism responsible for each process.



6. The following organisms have important roles as symbionts with plants and fungi; describe the symbiotic relationship of each organism with its host: cyanobacteria, mycorrhizae, *Rhizobium*, *Frankia*.
7. Outline the treatment process for drinking water.
8. The following processes are used in wastewater treatment. Match the stage of treatment with the processes. Each choice can be used once, more than once, or not at all.

Processes	Treatment Stage
_____ a. Leaching field	1. Primary
_____ b. Removal of solids	2. Secondary
_____ c. Biological degradation	3. Tertiary
_____ d. Activated sludge system	
_____ e. Chemical precipitation of phosphorus	
_____ f. Trickling filter	
_____ g. Results in drinking water	

9. *Bioremediation* refers to the use of living organisms to remove pollutants. Describe three examples of bioremediation.
10. NAME IT These nitrogen-fixing prokaryotes provide nitrogen fertilizer in rice paddies; they live symbiotically in the cells of the freshwater plant *Azolla*.

Multiple Choice

For questions 1–4, answer whether
- **a.** the process takes place under aerobic conditions
- **b.** the process takes place under anaerobic conditions.
- **c.** the amount of oxygen doesn't make any difference

1. Activated sludge system
2. Denitrification
3. Nitrogen fixation
4. Methane production
5. The water used to prepare intravenous solutions in a hospital contained endotoxins. Infection control personnel performed plate counts to find the source of the bacteria. Their results:

	Bacteria/100 ml
Municipal water pipes	0
Boiler	0
Hot water line	300

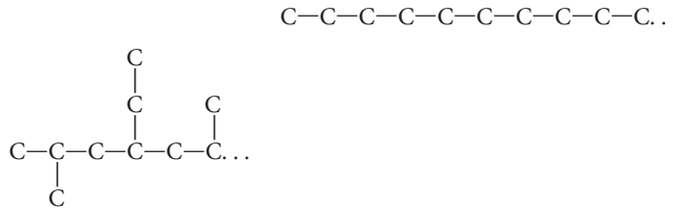
All of the following conclusions about the bacteria can be drawn *except* which one?
- **a.** They were present as a biofilm in the pipes.
- **b.** They are gram-negative.
- **c.** They come from fecal contamination.
- **d.** They come from the city water supply.
- **e.** none of the above

Use the following choices to answer questions 6–8:
- **a.** aerobic respiration
- **b.** anaerobic respiration
- **c.** anoxygenic photosynthesis
- **d.** oxygenic photosynthesis

6. $CO_2 + H_2S \xrightarrow{\text{Light}} \text{Light } C_6H_{12}O_6 + S^0$
7. $SO_4^{2-} + 10H^+ + 10e^- \longrightarrow H_2S + 4H_2O$
8. $CO_2 + 8H^+ + 8e^- \longrightarrow CH_4 + 2H_2O$
9. All of the following are effects of water pollution *except*
   - **a.** the spread of infectious diseases.
   - **b.** increased eutrophication.
   - **c.** increased BOD.
   - **d.** increased growth of algae.
   - **e.** none of the above
10. Coliforms are used as indicator organisms of sewage pollution because
    - **a.** they are pathogens.
    - **b.** they ferment lactose.
    - **c.** they are abundant in human intestines.
    - **d.** they grow within 48 hours.
    - **e.** all of the above

Analysis

1. Here are the formulas of two detergents that have been manufactured:



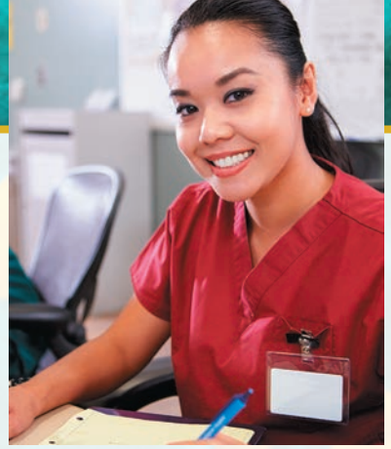
Which of these would be resistant, and which would be readily degraded by microorganisms? (*Hint:* Refer to the degradation of fatty acids in Chapter 5.)

2. Explain the effect of dumping untreated sewage into a pond on the eutrophication of the pond. The effect of sewage that has primary treatment? The effect of sewage that has secondary treatment? Contrast your previous answers with the effect of each type of sewage on a fast-moving river.

Clinical Applications and Evaluation

1. Flooding after two weeks of heavy rainfall in Tooele, Utah, preceded a high rate of diarrheal illness. *Giardia intestinalis* was isolated from 25% of the patients. A comparison study of a town 65 miles away revealed diarrheal illness in 2.9% of the 103 people interviewed. Tooele has a municipal water system and a municipal sewage treatment plant. Explain the probable cause of this epidemic and method(s) of stopping it. What would a fecal coliform test have shown?
2. The bioremediation process shown in the photograph is used to remove benzene and other hydrocarbons from soil contaminated by petroleum. The pipes are used to add nitrates, phosphates, oxygen, or water. Why are each of these added? Why is it not always necessary to add bacteria?





In the Clinic

As a nurse with the CDC's Epidemic Intelligence Service, you are notified of two Minnesota patients with listeriosis. You query the database and find three more cases in Illinois, Indiana, and Ohio. You confirm that all five had eaten a soft-ripened Brie cheese from the same manufacturer. Pasteurized milk was used to make the cheese, and a wine-vinegar solution was brushed on the cheese daily during fermentation. **What causes listeriosis? How can contamination occur after pasteurization?**

Hint: Read about food microbiology on pages 795–801.

Note: Answers to In the Clinic questions are found online at MasteringMicrobiology.

28 Applied and Industrial Microbiology

In Chapter 27, we saw that microbes are an essential factor in many natural phenomena that make life possible on Earth. In this chapter we will look at how microorganisms are harnessed in such useful applications as the making of food and industrial products. Many of these processes—especially baking, winemaking, brewing, and cheesemaking—have origins long lost in history.

Modern civilization, with its large urban populations, could not be supported without methods of preserving food. In fact, civilization arose only after agriculture produced a year-round, stable food supply so that people were able to give up a nomadic hunting-and-gathering way of life.

In Chapter 9, we discussed industrial applications of genetically modified microorganisms that are at the cutting edge of our knowledge of molecular biology. Many of these applications are now essential to modern industry. (See the Applications of Microbiology box in Chapter 1, page 3.) In this chapter, we will explore the microbial production of foods, drugs, and chemicals. The Clinical Case shows the role of microbiologists in ensuring that pathogens such as *Salmonella* (in the photo) are not in foods.

***Salmonella enterica* serovar.**

Food Microbiology

LEARNING OBJECTIVES

28-1 Describe thermophilic anaerobic spoilage and flat sour spoilage by mesophilic bacteria.

28-2 Compare and contrast food preservation by industrial food canning, aseptic packaging, radiation, and high pressure.

28-3 Name four beneficial activities of microorganisms.

Many of the methods of food preservation used today were probably discovered by chance in centuries past. People in early cultures observed that dried meat and salted fish resisted decay. Nomads must have noticed that soured animal milk resisted further decomposition and was still palatable. Moreover, if the curd of the soured milk was pressed to remove moisture and allowed to ripen (in effect, cheesemaking), it was even more effectively preserved and tasted better. Farmers soon learned that if grains were kept dry, they did not become moldy.

Foods and Disease

As more food products are being prepared at central facilities and widely distributed, it is becoming more likely that food, like municipal water supplies, might be a source of widespread disease outbreaks. To minimize the potential for disease outbreaks, communities have established local agencies whose role is to inspect dairies and restaurants. The United States Food and Drug Administration (FDA) and Department of Agriculture (USDA) also maintain a system of inspectors at ports and central processing locations. A recent development in this field has been the introduction of the **Hazard Analysis and Critical Control Point (HACCP)** system, which is intended to safeguard food "from farm to fork." Before the introduction of the HACCP system, the primary role of governmental agencies was to conduct sampling to identify contaminated foods. Such sampling to identify contamination will still have its place, but the HACCP system is designed to prevent contamination by identifying points at which foods are most likely to be contaminated with harmful microbes. Monitoring of these control points can prevent such microbes from being introduced or, if they are present, arrest their proliferation. For example, the HACCP system can identify steps during processing at which meats are likely to become contaminated by the animal's intestinal contents. The HACCP system also requires monitoring of adequate temperatures to kill pathogens during processing and adequate storage temperatures to prevent their reproduction.

Industrial Food Canning

In Chapter 7, you learned that preserving foods by heating a properly sealed container, as in home canning, is not difficult. The challenge in commercial canning is to use the right amount of heat necessary to kill spoilage organisms and dangerous microbes, such as the endospore-forming *Clostridium botulinum,* without degrading the appearance and palatability of food. Thus, much research is applied to determining the exact minimum heat treatment that will accomplish both these goals.

Industrial food canning is much more technically sophisticated than home canning (Figure 28.1). Industrially canned goods undergo **commercial sterilization** by steam under pressure in a large **retort,** which operates on the same principle as an autoclave (see Figure 7.2, page 181). Commercial sterilization is intended to destroy *C. botulinum* endospores and is not as rigorous as complete sterilization. The reasoning is that if *C. botulinum* endospores are destroyed, then any other significant spoilage or pathogenic bacteria will also be destroyed.

To ensure commercial sterilization, enough heat is applied for the **12D treatment** (12-decimal reductions, or *botulinal cook*), by which a theoretical population of *C. botulinum* endospores would be decreased by 12 logarithmic cycles. (See Figure 7.1 and Table 7.2, page 178.) What this means is that if there were 10^{12} (1,000,000,000,000) endospores in a can, after treatment there would be only one survivor. Because 10^{12} is an improbably large population, this treatment is considered quite safe. Certain thermophilic endospore-forming bacteria have endospores that are more resistant to heat treatment than those of *C. botulinum*. However, these bacteria are obligate thermophiles and generally remain dormant at temperatures lower than about 45°C. Therefore, they are not a spoilage problem at normal storage temperatures.

Spoilage of Canned Food

If canned foods are incubated at high temperatures, such as in a truck in the hot sun or next to a steam radiator, the thermophilic bacteria that often survive commercial sterilization can germinate and grow. **Thermophilic anaerobic spoilage** is therefore a fairly common cause of spoilage in low-acid canned foods. The can usually swells from gas, and the contents have a lowered pH and a sour odor. A number of thermophilic species of *Clostridium* can cause this type of spoilage. When thermophilic spoilage occurs but the can is not swollen by gas production, the spoilage is termed **flat sour spoilage.** This type of spoilage is caused by

Clinical Case: Dr. Chang and the Chocolate Factory

Dr. Derrick Chang of the CDC is alerted by PulseNet, the national molecular subtyping network for foodborne disease surveillance. PulseNet has identified an increase of genetically identical *Salmonella typhimurium* in the United States. This increase shows 120 isolates from 23 states in the last 60 days.

What is causing this outbreak? Read on to find out.

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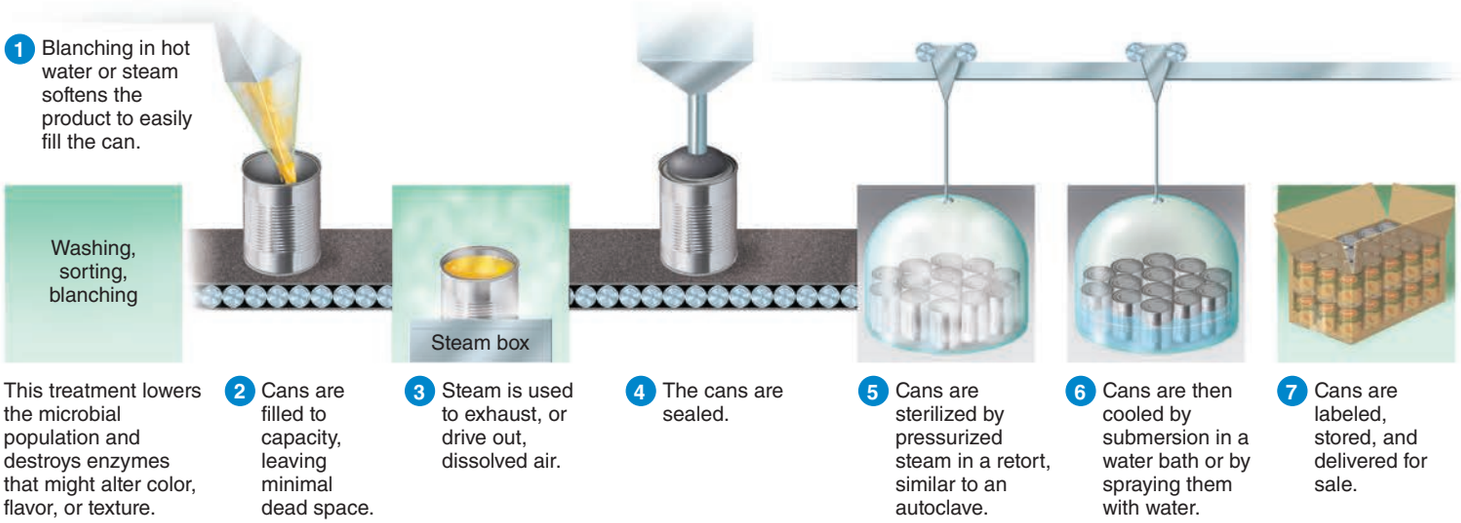


Figure 28.1 The commercial sterilization process in industrial canning.

Q How does commercial sterilization differ from complete sterilization?

thermophilic organisms such as *Geobacillus stearothermophilus* (jē′ō-bah-SIL-lus ste-rō′ther-MAH-fil-us), which is found in the starch and sugars used in food preparation. Many industries have standards for the numbers of such thermophilic bacteria permitted in raw materials. Both types of spoilage occur only when the cans are stored at higher than normal temperatures, which permits the growth of bacteria whose endospores are not destroyed by normal processing.

Mesophilic bacteria can spoil canned foods if the food is underprocessed or if the can leaks. Underprocessing is more likely to result in spoilage by endospore formers; the presence of non–endospore-forming bacteria strongly suggests that the can leaks. Leaking cans are often contaminated during the cooling of cans after processing by heat. The hot cans are sprayed with cooling water or passed through a trough filled with water. As the can cools, a vacuum is formed inside, and external water can be sucked through a leak past the heat-softened sealant in the crimped lid (Figure 28.2). Contaminating bacteria in the cooling water are drawn into the can with the water. Spoilage from underprocessing or can leakage is likely to produce odors of putrefaction, at least in high-protein foods, and occurs at normal storage temperatures. In such types of spoilage, there is always the potential that botulinal bacteria will be present.

Some acidic foods, such as tomatoes or preserved fruits, are preserved by processing temperatures of 100°C or lower. The reasoning is that the only spoilage organisms that will grow in such acidic foods are easily killed by even 100°C temperatures. Primarily, these would be molds, yeasts, and certain vegetative bacteria.

Occasional problems in acidic foods develop from a few microorganisms that are both heat resistant and acid tolerant. Examples of heat-resistant fungi are the mold *Byssochlamys fulva* (bis-sō-KLA-mis FUL-vah), which produces a *heat-resistant ascospore,* and a few molds, especially species of *Aspergillus,* that

Figure 28.2 The construction of a metal can. Notice the seam construction, which was introduced about 1904. During cooling after sterilization (see Figure 28.1, step 6), the vacuum formed in the can may actually force contaminating organisms into the can along with water.

Q Why isn't the can sealed before it is placed in the steam box?

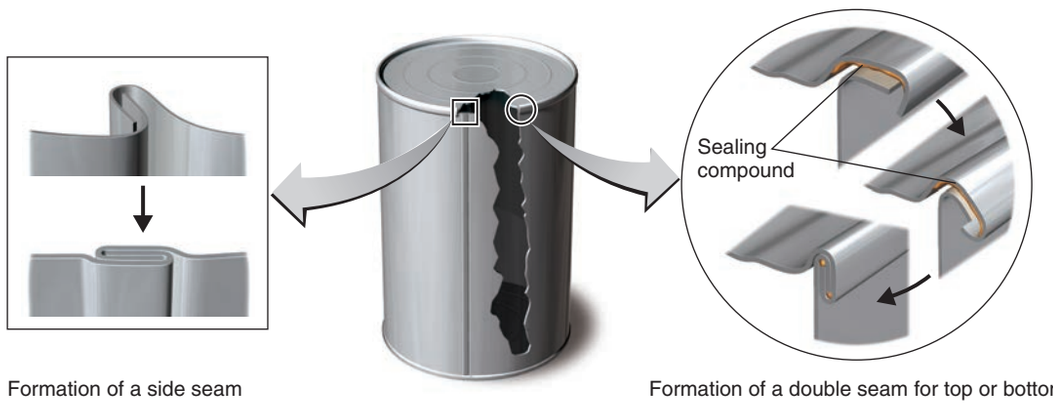


TABLE 28.1 Approximate Doses of Radiation Needed to Kill Various Organisms (Prions Are Not Affected)

Organisms	Dose (kGy)*
Higher animals (whole body)	0.005–0.1
Insects	0.01–1
Non–endospore-forming bacteria	0.5–10
Bacterial endospores	10–50
Viruses	10–200

*Gray is a measure of ionizing irradiation; kGy is 1000 Grays.

Source: J. Farkas, "Physical Methods of Food Preservation," in *Food Microbiology: Fundamentals and Frontiers,* 2d ed., M.P. Doyle et al. (Eds) (Washington, DC: ASM Press, 2001).

sometimes produce specialized resistant bodies called *sclerotia*. A spore-forming bacterium, *Bacillus coagulans* (bah-SIL-lus kō-AG-ū-lanz), is unusual in that it is capable of growth at a pH of almost 4.0.

Aseptic Packaging

The use of **aseptic packaging** to preserve food has been increasing. Packages are usually made of some material that cannot tolerate conventional heat treatment, such as laminated paper or plastic. The packaging materials come in continuous rolls that are fed into a machine that sterilizes the material with a hot hydrogen peroxide solution, sometimes aided by ultraviolet (UV) light. Metal containers can be sterilized with superheated steam or other high-temperature methods. High-energy electron beams can also be used to sterilize the packaging materials. While still in the sterile environment, the material is formed into packages, which are then filled with liquid foods that have been conventionally sterilized by heat. The filled package is not sterilized after it is sealed.

Radiation and Industrial Food Preservation

It has long been recognized that irradiation is lethal to microorganisms; in fact, a patent was issued in Great Britain in 1905 for the use of ionizing radiation to improve the condition of foodstuffs. X rays were specifically suggested in 1921 as a way to inactivate the larvae in pork that are the cause of trichinellosis. Ionizing irradiation inhibits DNA synthesis and effectively prevents microorganisms, insects, and plants from reproducing. The ionizing irradiation is usually X rays or the gamma rays produced by radioactive cobalt-60. Up to certain energy levels, high-energy electrons produced by electron accelerators are also used. The main practical difference is in penetration capabilities. These sources inactivate the target organisms and do *not* induce radioactivity in the food or packaging material. The relative doses of radiation needed to kill various organisms are presented in Table 28.1. Radiation is measured in *Grays,* named for an early radiologist—often in terms of thousands of Grays, abbreviated as kGy.

- *Low doses of irradiation (less than 1 kGy)* are used to kill insects (disinfestation) and inhibit sprouting, as in stored potatoes. Similarly, it can delay ripening of fruits during storage.
- *Pasteurizing doses (1 to 10 kGy)* can be used on meats and poultry to eliminate or critically reduce the numbers of specific bacterial pathogens.
- *High doses (more than 10 kGy)* are used to sterilize, or at least greatly lower, the bacterial populations in many spices. Spices are often contaminated with 1 million or more bacteria per gram, although these are not considered to be normally hazardous to health.

A specialized use of irradiation has been to sterilize meats eaten by American astronauts, and a few health facilities have selectively used irradiation to sterilize foods ingested by immunocompromised patients. Millions of implanted medical devices, such as pacemakers, have been irradiated. Irradiated food is marked in the United States with a radura symbol and a printed notice. Unfortunately, this symbol has often been interpreted as a warning rather than the description of an approved processing treatment or preservative. In fact, irradiated foods

Clinical Case

Dr. Chang initiates a case-control study with representatives of the state health departments that had reported *S. typhimurium* infections. Fifteen items, suspected as possible vehicles of infection on the basis of the individual case investigations, are listed. State officials determine whether each suspect item was used or consumed by the infected person within the 3 days before onset of illness. The family of each patient identifies two neighborhood controls, of the same age and gender as the patient. Controls were asked the same questions as patients, except that they were questioned about the use or consumption of the 15 suspect items during the previous month. Some of the data collected are shown in the table.

Foil-Wrapped Chocolate Balls	Cases	Controls
Ate	38	12
Did not eat	7	79

Calculate the relative risk for this food item.
(Hint: See page 717)

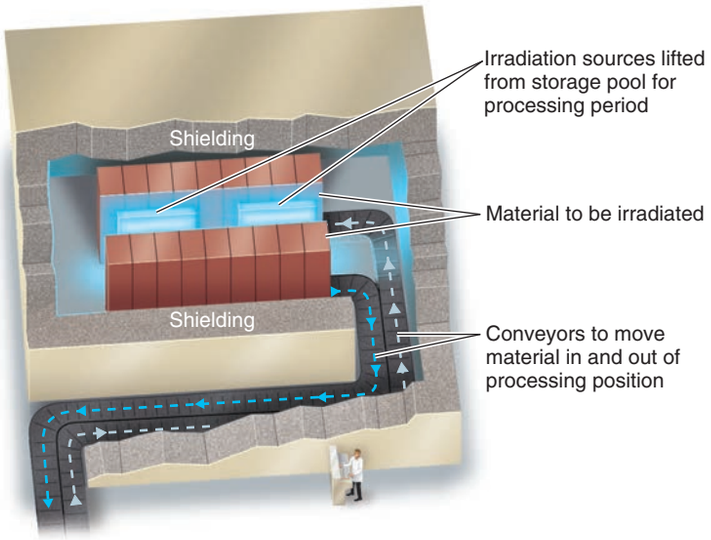


Figure 28.3 A gamma-ray irradiation facility. Shown is the path of the material to be irradiated.

Q Can microwaves be used to sterilize foods?

are not radioactive; consider that the X-ray table in a hospital does not become radioactive from repeated daily exposure to ionizing radiation. Recently, the FDA has allowed, upon special approval, substitution of language such as "pasteurization" rather than "irradiation."

When deep penetration is a requirement, the preferred method for irradiation is gamma rays produced by cobalt-60. However, this type of treatment requires several hours of exposure in isolation behind protective walls (Figure 28.3).

High-energy electron accelerators (Figure 28.4) are much faster and sterilize in a few seconds, but this treatment has low penetrating power and is suitable only for sliced meats, bacon, or similar thin products. Also, plasticware used in microbiology is usually sterilized in this way. Another recent application is to irradiate mail to kill possible bioterrorism agents that it might contain, such as anthrax endospores.

High-Pressure Food Preservation

A recent development in food preservation has been the use of a high-pressure processing technique (*pascalization*). Prewrapped foods such as fruits, deli meats, and precooked chicken strips are submerged into tanks of pressurized water. The pressure can reach 87,000 pounds per square inch (psi)—which has been compared to the equivalent of about three elephants standing on a dime. This process kills many bacteria, such as *Salmonella, Listeria,* and pathogenic strains of *E. coli,* by disrupting many cellular functions. It also kills nonpathogenic microorganisms that tend to shorten the shelf life of such products.

Because the process does not require additives, it does not require regulatory approval. It has the advantage of preserving colors and tastes of foods better than many other methods and does not provoke the concerns of irradiation.

The Role of Microorganisms in Food Production

In the latter part of the nineteenth century, microbes used in food production were grown in pure culture for the first time. This development quickly led to an improved understanding of the relationships between specific microbes and their products and activities. This period can be considered the beginning of industrial food microbiology. For example, once it was understood that a certain yeast grown under certain conditions produced beer and that certain bacteria could spoil the beer, brewers were better able to control the quality of their products. Specific industries became active in microbiological research and selected certain microbes for their special qualities. The brewing industry extensively investigated the isolation and identification of yeasts and selected those that could produce more alcohol. In this section, we will discuss the role of microorganisms in the production of several common foods.

Cheese

The United States leads the world in the making of cheese, producing millions of tons every year. Although there are many types of cheeses, all require the formation of a **curd,** which can be

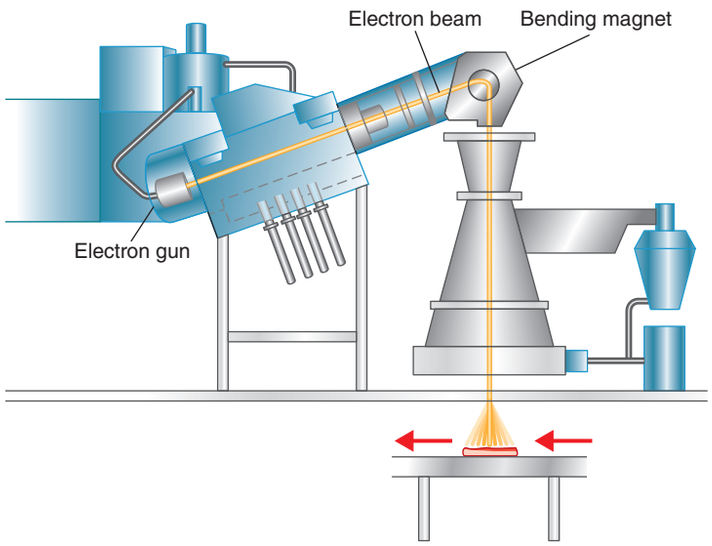


Figure 28.4 Electron-beam accelerator. These machines generate an electron stream that is accelerated down a long tube by electromagnets of the opposite charge. In the drawing, the electron beam is bent by a "bending magnet." This serves to filter out electrons of unwanted energy levels, providing a beam of uniform energy. The vertical beam is swept back and forth over the target as it is moved past the beam. The penetrating power of the beam is limited: if the target substance is expressed as an equivalent thickness of water, the maximum is about 3.9 cm (1.5 in). In contrast, X rays will penetrate about 23 cm (9 in).

Q Are high-energy electrons ionizing radiation?

separated from the main liquid fraction, or **whey** (Figure 28.5). The curd is made up of a protein, **casein,** and is usually formed by the action of an enzyme, **rennin** (or chymosin), which is aided by acidic conditions provided by certain lactic acid–producing bacteria. These inoculated lactic acid bacteria also provide the characteristic flavors and aromas of fermented dairy products during the ripening process. The curd undergoes a microbial ripening process, except in the case of a few unripened cheeses, such as ricotta and cottage cheese.

Cheeses are generally classified by their hardness, which is produced in the ripening process. The more moisture lost from the curd and the more the curd is compressed, the harder the cheese.

The hard cheddar and Swiss cheeses are ripened by lactic acid bacteria growing anaerobically in the interior. Such hard, interior-ripened cheeses can be quite large. The longer the incubation time, the higher the acidity and the sharper the taste of the cheese. A *Propionibacterium* (prō-pē′on-ē-bak-TI-rē-um) species produces carbon dioxide, which forms the holes in Swiss cheese. Semisoft cheeses, such as Limburger, are ripened by bacteria and other contaminating organisms growing on the surface. Blue and Roquefort cheeses are ripened by *Penicillium* molds inoculated into the cheese. The texture of the cheese is loose enough that adequate oxygen can reach the aerobic molds. The growth of the *Penicillium* molds is visible as blue-green clumps in the cheese. Camembert, a soft cheese, is ripened in small packets so that the enzymes of *Penicillium* mold growing aerobically on the surface will diffuse into the cheese for ripening. The Applications of Microbiology box on page 801 describes one use of the whey produced as a by-product by the dairy industry.

Other Dairy Products

Butter is made by churning cream until the fatty globules of butter separate from the liquid *buttermilk*. The typical flavor and aroma of butter and buttermilk are from *diacetyls,* a combination of two acetic acid molecules that is a metabolic end-product of fermentation by some lactic acid bacteria. Today, commercially sold buttermilk is usually not a by-product of buttermaking but is made by inoculating skim milk with bacteria that form lactic acid and the diacetyls. *Cultured sour cream* is made from cream inoculated with microorganisms similar to those used to make buttermilk.

Yogurt, a slightly acidic dairy product, is found around the world and is popular in the United States. Commercial yogurt is made from milk, from which at least one-fourth of the water has been evaporated in a vacuum pan. The resulting thickened milk is inoculated with a mixed culture of *Streptococcus thermophilus,* primarily for acid production, and *Lactobacillus delbrueckii bulgaricus* (bul-GAR-i-kus), to contribute flavor and aroma. The temperature of the fermentation is about 45°C for several hours, during which time *S. thermophilus* outgrows *L. d. bulgaricus*. Maintaining the proper balance between the flavor-producing and the acid-producing microbes is the secret of making yogurt.



The milk has been coagulated by the action of rennin (forming curd) and is inoculated with ripening bacteria for flavor and acidity. The curd is chopped into small cubes to facilitate efficient draining of whey.

Figure 28.5 Making cheddar cheese.

Q Are there living bacteria in the final cheese product?

Kefir and *kumiss* are fermented milk beverages that are popular in eastern Europe. The usual lactic acid–producing bacteria are supplemented with a lactose-fermenting yeast to give these drinks an alcohol content of 1–2%.

Nondairy Fermentations

Historically, milk fermentation allowed dairy products to be stored and then consumed much later. Other microbial fermentations were used to make certain plants edible. For example, pre-Columbian people in Central and South America learned to ferment cacao beans before consumption. The microbial products released during fermentation produce the chocolate flavor.

Microorganisms are also used in baking, especially for bread. The sugars in bread dough are fermented by yeasts. The species of yeast used in baking is *Saccharomyces cerevisiae*. This same species of yeast is also used in the brewing of beer from grains and the fermentation of wines from grapes. (At one time *S. cerevisiae* was classified as multiple species, such as *S. pastorianus, S. uvarum,* and *S. c. ellipsoideus;* these and a few other species names are often encountered in older literature.) *S. cerevisiae* will grow readily under both aerobic and anaerobic conditions, although, unlike facultatively anaerobic bacteria such as *E. coli,* it cannot grow anaerobically indefinitely. Various strains of *S. cerevisiae* have been developed over the centuries and are highly adapted to certain fermentation uses.

Anaerobic conditions for producing ethanol by the yeasts are mandatory for producing alcoholic beverages. In baking, carbon dioxide forms the typical bubbles of leavened bread. Aerobic conditions favor carbon dioxide production and are encouraged as much as possible. This is the reason bread dough is kneaded repeatedly. Whatever ethanol is produced evaporates during baking. In some breads, such as rye or sourdough, the growth of lactic acid bacteria produce the typical tart flavor.

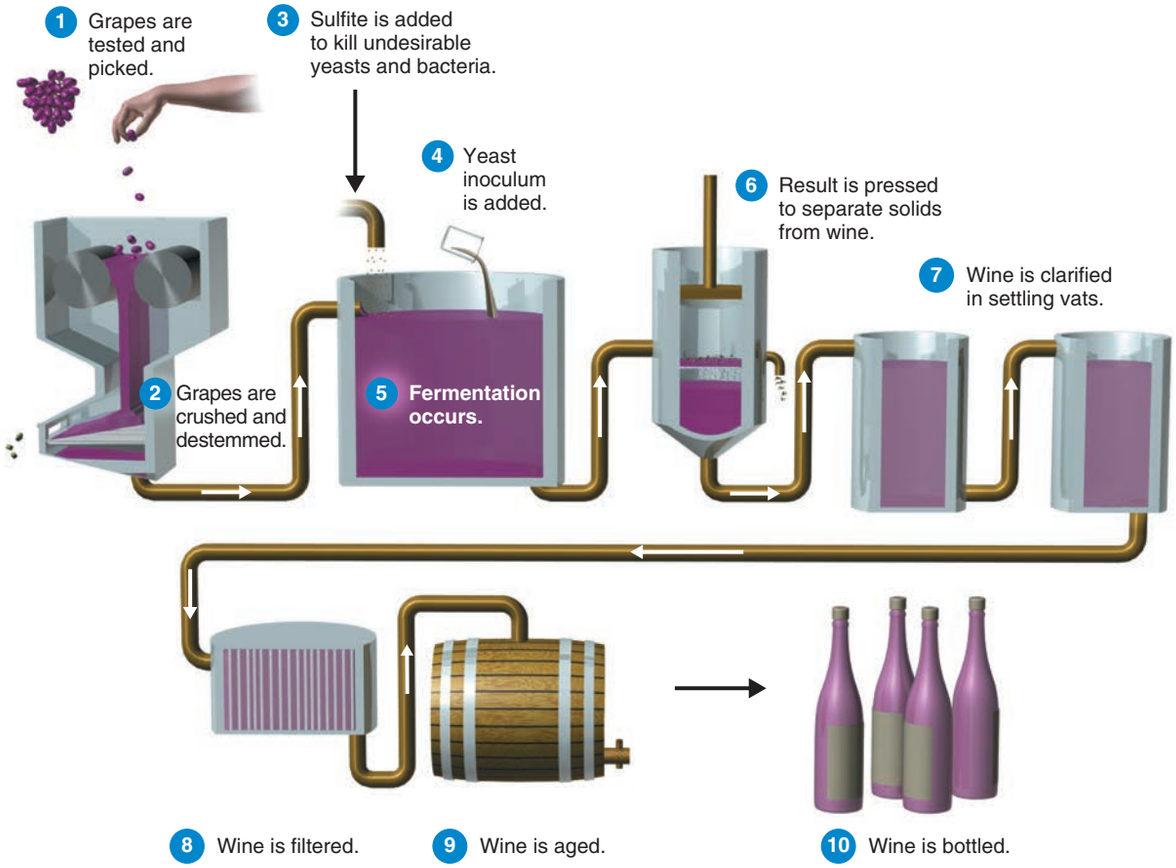


Figure 28.6 The basic steps in making red wine. For white wines, the pressing precedes fermentation so that the color is not extracted from the solid matter.

What happens if air enters at step 5? At step 10?

Fermentation is also used in the production of such foods as *sauerkraut, pickles, olives,* and even chocolate and coffee, in which the beans undergo a fermentation step.

Alcoholic Beverages and Vinegar

Microorganisms are involved in the production of almost all alcoholic beverages. Beer and ale are products of grain starches fermented by yeast. **Beer** is fermented slowly with yeast strains that remain on the bottom (*bottom yeasts*). Ale is fermented relatively rapidly, at a higher temperature, with yeast strains that usually form clumps that are buoyed to the top by CO_2 (*top yeasts*). Because yeasts are unable to use starch directly, the starch from grain must be converted to glucose and maltose, which the yeasts can ferment into ethanol and carbon dioxide. In this conversion, called **malting,** starch-containing grains, such as malting barley, are allowed to sprout and then are dried and ground. This product, called **malt,** contains starch-degrading enzymes (amylases) that convert cereal starches into carbohydrates that can be fermented by yeasts. Light beers use amylases or selected strains of yeast to convert more of the starch to fermentable glucose and maltose, resulting in fewer carbohydrates and more alcohol. The beer is then diluted to arrive at an alcohol percentage in the usual range. **Sake,** the Japanese rice wine, is made from rice without malting because the mold *Aspergillus* is first used to convert the rice's starch to sugars that can be fermented. (See the discussion of koji, page 804.) For *distilled spirits,* such as *whiskey, vodka,* and *rum,* carbohydrates from cereal grains, potatoes, and molasses are fermented to alcohol. The alcohol is then distilled to make a concentrated alcoholic beverage.

Wines are made from fruits, typically grapes, that contain sugars that yeasts can use directly for fermentation; malting is unnecessary in winemaking. Grapes usually need no additional sugars, but other fruits might be supplemented with sugars to ensure enough alcohol production. The steps of winemaking are shown in Figure 28.6. Lactic acid bacteria are important when wine is made from grapes that are especially acidic from high concentrations of malic acid. These bacteria convert the malic acid to the weaker lactic acid in a process called **malolactic fermentation.** The result is a less acidic, better-tasting wine than would otherwise be produced.

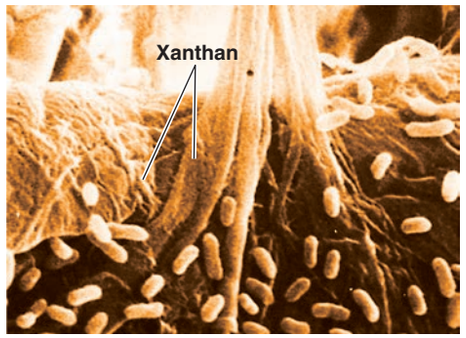
From Plant Disease to Shampoo and Salad Dressing

Xanthomonas campestris is a gram-negative rod that causes a disease called black rot in plants. After gaining access to a plant's vascular tissues, the bacteria use the glucose transported in those tissues to produce a sticky, gumlike substance. This substance builds up to form gumlike masses, which eventually block the plant's transport of nutrients. The gum that makes up these masses, xanthan, is composed of a high-molecular-weight polymer of mannose (see the photograph).

In contrast to its effects in plants, xanthan has no adverse effects when ingested by humans. Consequently, xanthan can be used as a thickener in dairy products, salad dressings, cosmetics, cold creams, and shampoos.

The average American consumes more than 30 pounds of cheese annually, and every pound of cheese creates 9 pounds of the liquid by-product called whey. When researchers at the U.S. Department of Agriculture (USDA) wanted to find some useful product that could be made out of whey, they thought of turning it into xanthan. However, because whey is mostly water and lactose, researchers had to figure out how to get *X. campestris* to produce xanthan using lactose rather than glucose.

A research team working with the USDA at Stauffer Chemical Company used an enrichment based on satisfying only two requirements: that the bacteria grow on whey and that they make xanthan. First, they inoculated a whey medium with *X. campestris* and incubated it for 24 hours. Then they transferred an inoculum of this culture to a flask of lactose broth, to select a lactose-utilizing cell. The strain did not have to make xanthan from this broth; it only had to grow and use lactose. A lactose-utilizing strain was isolated through serial transfers, selecting for the strain with the best ability to grow. After incubation for 10 days, an inoculum was transferred to another flask of lactose broth, and the procedure was repeated two more times. When transferred to a flask of whey medium, the final lactose-utilizing bacteria grew in the whey, and the culture became extremely viscous—xanthan was being produced.



***Xanthomonas campestris* producing gooey xanthan.**

The final result was a process in which 40 g/L of whey powder is converted into 30 g/L of xanthan gum. A quick survey of labels in your neighborhood supermarket will demonstrate just how successful this project was.

Clinical Case

Illness due to *S. typhimurium* infection has a high association with consumption of foil-wrapped chocolate balls (relative risk = 9.3). Dr. Chang initiates environmental testing and trace-back to locate the source of contamination. From questioning families and examining store invoices, investigators identify the specific chocolate item (identified by the manufacturer's code number). State health department laboratories find that at least 22 of these chocolate samples contain *S. typhimurium*.

How will Dr. Chang find the source of contamination?

795 797 801 804 806 807

Wine producers who allowed wine to be exposed to air found that it soured from the growth of aerobic bacteria that converted the ethanol in the wine to acetic acid. The result was *vinegar* (*vin* = wine; *aigre* = sour). The process is now used deliberately to make vinegar. Ethanol is first produced by anaerobic fermentation of carbohydrates by yeasts. The ethanol is then aerobically oxidized to acetic acid by acetic acid–producing bacteria of the genera *Acetobacter* and *Gluconobacter.*

CHECK YOUR UNDERSTANDING

- Is botulism a greater danger in spoilage of canned goods under thermophilic or under mesophilic conditions? **28-1**
- Canned foods are usually in metal cans. What sorts of containers are used for aseptically packaged foods? **28-2**
- Roquefort and blue cheeses are characterized by blue-green clumps. What are these? **28-3**

Industrial Microbiology

LEARNING OBJECTIVES

28-4 Define *industrial fermentation* and *bioreactor.*

28-5 Differentiate primary from secondary metabolites.

28-6 Describe the role of microorganisms in the production of industrial chemicals and pharmaceuticals.

28-7 Define *bioconversion,* and list its advantages.

28-8 List biofuels that can be made by microorganisms.

The industrial uses of microbiology had their beginnings in large-scale food fermentations that produced lactic acid from

dairy products and ethanol from brewing. These two chemicals also proved to have many industrial uses unrelated to foods. During World Wars I and II, microbial fermentation and similar technologies were used in the production of armament-related chemical compounds, such as glycerol and acetone. Present industrial microbiology dates largely from the technology developed to produce antibiotics following World War II. There is renewed interest in some of these classic microbial fermentations, especially if they can be used as feedstocks, products that are renewable, or, ideally, use products that would otherwise be wasted.

In recent years, industrial microbiology has been revolutionized by **biotechnology,** the application of genetically modified organisms. An example of a genetically engineered *biosensor* to detect pollution is explained in the Applications of Microbiology box on page 783. In Chapter 9, we discussed the methods for making these modified organisms using recombinant DNA technology and described some of the products derived from them.

Fermentation Technology

The industrial production of microbial products usually involves fermentation. *Industrial fermentation* is the large-scale cultivation of microbes or other single cells to produce a commercially valuable substance. We have just discussed the most familiar examples: the anaerobic food fermentations used in the dairy, brewing, and winemaking industries. Much of the same technology, with the frequent addition of aeration, has been adapted to make other industrial products, such as insulin and human growth hormone, from genetically modified microorganisms. Industrial fermentation is also used in biotechnology to obtain useful products from genetically modified plant and animal cells (see Chapter 9). For example, animal cells are used to make monoclonal antibodies (see Chapter 18, page 501).

Vessels for industrial fermentation are called **bioreactors;** they are designed with close attention to aeration, pH control, and temperature control. There are many different designs, but the most widely used bioreactors are of the continuously stirred type (Figure 28.7). The air is introduced through a diffuser at the bottom (which breaks up the incoming airstream to maximize aeration), and a series of impeller paddles and stationary wall baffles keep the microbial suspension agitated. Oxygen is not very soluble in water, and keeping the heavy microbial suspension well aerated is difficult. Highly sophisticated designs have been developed to achieve maximum efficiency in aeration and other growth requirements, including medium formulation. The high value of the products of genetically modified microorganisms and eukaryotic cells has stimulated the development of newer types of bioreactors and computerized controls for them.

Bioreactors are sometimes very large, holding as much as 500,000 liters. When the product is harvested at the completion of the fermentation, this is known as *batch production.* There

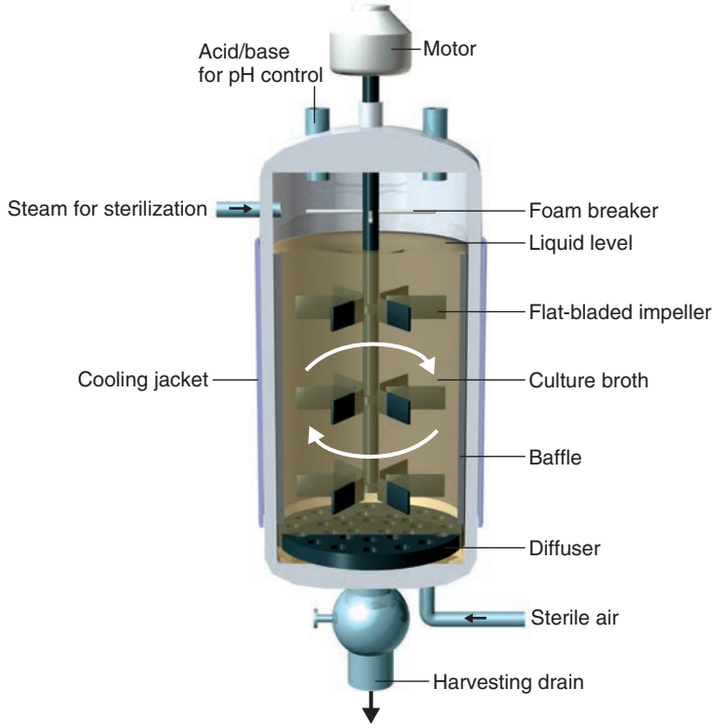


Figure 28.7 Section of a continuously stirred bioreactor for industrial fermentations.

Q Identify one essential difference between the bioreactor illustrated and a vat for making wine.

are other designs of fermentors. For *continuous flow production,* in which the substrates (usually a carbon source) are fed continuously past immobilized enzymes or into a culture of growing cells, spent medium and desired product are continuously removed.

Generally speaking, the microbes in industrial fermentation produce either primary metabolites, such as ethanol, or secondary metabolites, such as penicillin. A **primary metabolite** is formed essentially at the same time as the new cells, and the production curve follows the cell population curve almost in parallel, with only minimal lag. **Secondary metabolites** are not produced until the microbe has largely completed its logarithmic growth phase, known as the **trophophase,** and has entered the stationary phase of the growth cycle. The following period, during which most of the secondary metabolite is produced, is known as the **idiophase.** The secondary metabolite may be a microbial conversion of a primary metabolite. Alternatively, it may be a metabolic product of the original growth medium that the microbe makes only after considerable numbers of cells and a primary metabolite have accumulated. Cellular metabolism leaves behind small-molecule chemical fingerprints of the cellular processes: a metabolic profile. The use of these chemical fingerprints to study cellular processes involving metabolites is termed **metabolomics.**

Strain improvement is also an ongoing activity in industrial microbiology. (A microbial **strain** differs physiologically in some

significant way. For example, it has an enzyme to carry out some additional activity or lacks such an ability, but this difference is not enough to change its species identity.) A well-known example is that of the mold used for penicillin production. The original culture of *Penicillium* did not produce penicillin in large enough quantities for commercial use. A more efficient culture was isolated from a moldy cantaloupe from a Peoria, Illinois, supermarket. This strain was treated variously with UV light, X rays, and nitrogen mustard (a chemical mutagen). Selections of mutants, including some that arose spontaneously, quickly increased the production rates by a factor of more than 100. Today, the original penicillin-producing molds produce, not the original 5 mg/L, but 60,000 mg/L. Improvements in fermentation techniques have nearly tripled even this yield. An example of a strain that was developed by enrichment and selection is described in the Applications of Microbiology box on page 801.

Immobilized Enzymes and Microorganisms

In many ways, microbes are packages of enzymes. Industries are increasing their use of free enzymes isolated from microbes to manufacture many products, such as high-fructose syrups, paper, and textiles. The demand for such enzymes is high because they are specific and do not produce costly or toxic waste products. And, unlike traditional chemical processes that require heat or acids, enzymes work under moderate conditions and are safe and biodegradable. For most industrial purposes, the enzyme must be immobilized on the surface of some solid support or otherwise manipulated so that it can convert a continuous flow of substrate to product without being lost.

Continuous flow techniques have also been adapted to live whole cells, and sometimes even to dead cells (**Figure 28.8**). Whole-cell systems are difficult to aerate, and they lack the single-enzyme specificity of immobilized enzymes. However, whole cells are advantageous if the process requires a series of steps that can be carried out by one microbe's enzymes. They also have the advantage of allowing continuous flow processes with large cell populations operating at high reaction rates. Immobilized cells, which are usually anchored to microscopically small spheres or fibers, are currently used to make high-fructose syrup, aspartic acid, and numerous other products of biotechnology.

CHECK YOUR UNDERSTANDING

- Do bioreactors operate aerobically or anaerobically? **28-4**
- Penicillin is produced in its greatest quantities after the trophophase of fermentation. Does that make it a primary or secondary metabolite? **28-5**

Industrial Products

As mentioned earlier, cheesemaking produces an organic waste called whey. The whey must be disposed of as sewage or dried and burned as solid waste. Both of these processes are costly and ecologically problematic. However, microbiologists have discovered an alternative use for whey, as discussed in the Applications of Microbiology box on page 801. In this way, microbiologists are devising uses for old products and creating new ones. In this section, we will discuss some of the more important commercial microbial products and the growing alternative energy industry.

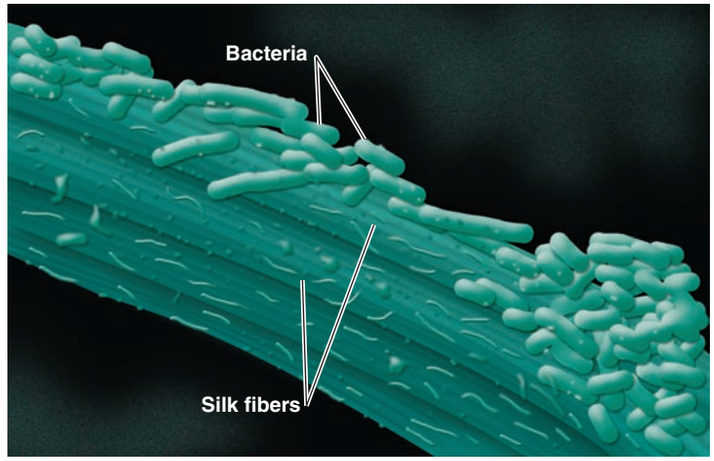


Figure 28.8 Immobilized cells. In some industrial processes, the cells are immobilized on surfaces such as the silk fibers shown here. The substrate flows past the immobilized cells.

Q How does this process resemble the action of a trickling filter in sewage treatment?

Amino Acids

Amino acids have become a major industrial product from microorganisms. For example, over 1 million tons of *glutamic acid* (L-glutamate), used to make the flavor enhancer monosodium glutamate, are produced every year. Certain amino acids, such as *lysine* and *methionine,* cannot be synthesized by animals and are present only at low levels in the normal diet. Therefore, the commercial synthesis of lysine and some of the other essential amino acids as cereal food supplements is an important industry. More than 250,000 tons each of lysine and methionine are produced every year.

Two microbially synthesized amino acids, *phenylalanine* and *aspartic acid* (L-aspartate), have become important as ingredients in the sugar-free sweetener aspartame (NutraSweet). Some 7000 to 8000 tons of each of these amino acids are produced annually in the United States.

In nature, microbes rarely produce amino acids in excess of their own needs because feedback inhibition prevents wasteful production of primary metabolites (see Chapter 5, page 116). Commercial microbial production of amino acids depends on specially selected mutants and sometimes on ingenious manipulations of metabolic pathways. For example, in applications in which only the L-isomer of an amino acid is desired, microbial production, which forms only the L-isomer, has an advantage

over chemical production, which forms both the **D-isomer** and the **L-isomer** (see Figure 2.13, page 40).

Citric Acid

Citric acid is a constituent of citrus fruits, such as oranges and lemons, and at one time these were its only industrial source. However, over 100 years ago, citric acid was identified as a product of mold metabolism. This discovery was first used as an industrial process when World War I interfered with the picking of the Italian lemon crop. Citric acid has an extraordinary range of uses beyond the obvious ones of giving tartness and flavor to foods. It is an antioxidant and pH adjuster in many foods, and in dairy products it often serves as an emulsifier. Over 1.6 million tons of citric acid are produced every year worldwide. Much of it is produced by a mold, *Aspergillus niger* (a-sper-JIL-lus NĪ-jer), with molasses used as a substrate.

Enzymes

Enzymes are widely used in different industries. For example, *amylases* are used in the production of syrups from corn starch, in the production of paper sizing (a coating for smoothness, as on this page), and in the production of glucose from starch. The microbiological production of amylase is considered to be the first biotechnology patent issued in the United States, which was given to the Japanese scientist Jokichi Takamine. The basic process by which molds were used to make an enzyme preparation known as **koji** had been used for centuries in Japan to make fermented soy products. Koji is an abbreviation of a Japanese word meaning bloom of mold, reflecting the infiltration of a cereal substrate, either rice or a wheat-soybean mixture, with a filamentous fungus (*Aspergillus*). Primarily, the amylases in koji change starch into sugars, but koji preparations also contain proteolytic enzymes that convert the protein in soybeans into a more digestible and flavorful form. It is the basis of soybean fermentations that are staples of the Japanese diet, such as *soy sauce* and *miso* (a fermented paste of soybeans with a meaty flavor). *Sake,* the well-known Japanese rice wine, makes use of amylases of koji to change the carbohydrates of rice into a form that yeasts can use to produce alcohol. This is roughly the equivalent of the barley malt (page 800) used in beer brewing.

Glucose isomerase is an important enzyme; it converts the glucose that amylases form from starches into fructose, which is used in place of sucrose as a sweetener in many foods. Probably half of the bread baked in this country is made with the aid of *proteases,* which adjust the amount of glutens (protein) in wheat so that baked goods are improved or made uniform. Other proteolytic enzymes are used as meat tenderizers or in detergents as an additive to remove proteinaceous stains. About a third of all industrial enzyme production is for this purpose. *Rennin,* an enzyme used to form curds in milk, is usually produced commercially by fungi but more recently by genetically modified bacteria. An example of a popular clothing product produced with enzymes is described in the Applications of Microbiology box in Chapter 1, page 3.

Vitamins

Vitamins are sold in large quantities combined in tablet, chewable, and liquid form and are used as individual food supplements. Microbes can provide an inexpensive source of

Clinical Case

The following ingredients are combined in the manufacturing of milk chocolate: cacao beans, cocoa butter (fat pressed out of the cacao bean), sugar, lecithin, vanillin, and salt. Cacao beans from Ghana, Nigeria, Brazil, and Ecuador are blended and roasted for 30 minutes at 125°C. The beans are then air cooled and ground. In the mixing room, the dry ingredients (salt, sugar, and ground beans) are blended and then mixed with the Brazilian cocoa butter in 3-ton batches for molding.

The factory microbiologist is responsible for ensuring that the raw ingredients are free of pathogens when they enter the factory. In the past, she has rejected coconut milk and eggs that tested positive for *Salmonella*. She recently rejected a peanut shipment that tested positive for mycotoxins. Dr. Chang asks the factory microbiologist to culture selected items in the production line. Her results are shown in the table.

	Number of Samples	Number Positive for *S. typhimurium*
Raw material storage area	56	0
Bean roasting room	16	2
Beans	14	0
Cocoa butter	9	0
Lecithin	7	0
Vanillin	1	0
Raw bean room	11	2
Mixing room	14	0
Trash room	7	0
Janitorial equipment	10	0
Chocolate molds	62	2
Tap water	5	0
Production line chocolate samples	25	0

Now where will Dr. Chang look?

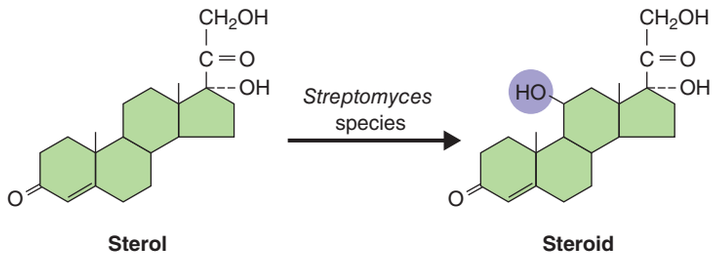


Figure 28.9 The production of steroids. Shown here is the conversion of a precursor compound such as a sterol into a steroid by *Streptomyces*. The addition of a hydroxyl group (highlighted in purple on the steroid) to carbon number 11 might require more than 30 steps by chemical means, but the microorganism can add it in only one step.

Q Name a commercial product that is a steroid.

some vitamins. *Vitamin* B_{12} is produced by *Pseudomonas* and *Propionibacterium* species. *Riboflavin* (B_2) is another vitamin produced by fermentation, mostly by fungi such as *Ashbya gossypii* (ASH-bē-ah gos-SIP-ē-ē). *Vitamin C* (ascorbic acid) is produced at the rate of 60,000 tons per year by a complicated modification of glucose by *Acetobacter* species.

Pharmaceuticals

Modern pharmaceutical microbiology developed after World War II, when production of antibiotics was introduced.

All antibiotics were originally the products of microbial metabolism. Many are still produced by microbial fermentations, and work continues on the selection of more productive mutants by nutritional and genetic manipulations. At least 6000 antibiotics have been described. One organism, *Streptomyces hygroscopius,* has different strains that make almost 200 different antibiotics. Antibiotics are typically made industrially by inoculating a solution of growth medium with spores of the appropriate mold or streptomycete and vigorously aerating it.

Vaccines are a product of industrial microbiology. Many antiviral vaccines are mass-produced in chicken eggs or cell cultures. The production of vaccines against bacterial diseases usually requires the growth of large amounts of the bacteria. Recombinant DNA technology is increasingly important in the development and production of subunit vaccines (see Chapter 18, page 496).

Steroids are a very important group of chemicals that include *cortisone,* which is used as an anti-inflammatory drug, and *estrogens* and *progesterone,* which are used in oral contraceptives. Recovering steroids from animal sources or chemically synthesizing them is difficult, but microorganisms can synthesize steroids from sterols or from related, easily obtained compounds. For example, Figure 28.9 illustrates the conversion of a sterol into a valuable steroid.

Copper Extraction by Leaching

Acidithiobacillus ferrooxidans is used in recovering otherwise unprofitable grades of copper ore, which sometimes contain as little as 0.1% copper. At least 25% of the world's copper is produced this way. *Acidithiobacillus* bacteria get their energy from the oxidation of a reduced form of iron (Fe^{2+}) in ferrous sulfide to an oxidized form (Fe^{3+}) in ferric sulfate. Sulfuric acid (H_2SO_4) is also a product of the reaction. The acidic solution of Fe^{3+}-containing water is applied by sprinklers and allowed to percolate downslope through the ore body (Figure 28.10). The

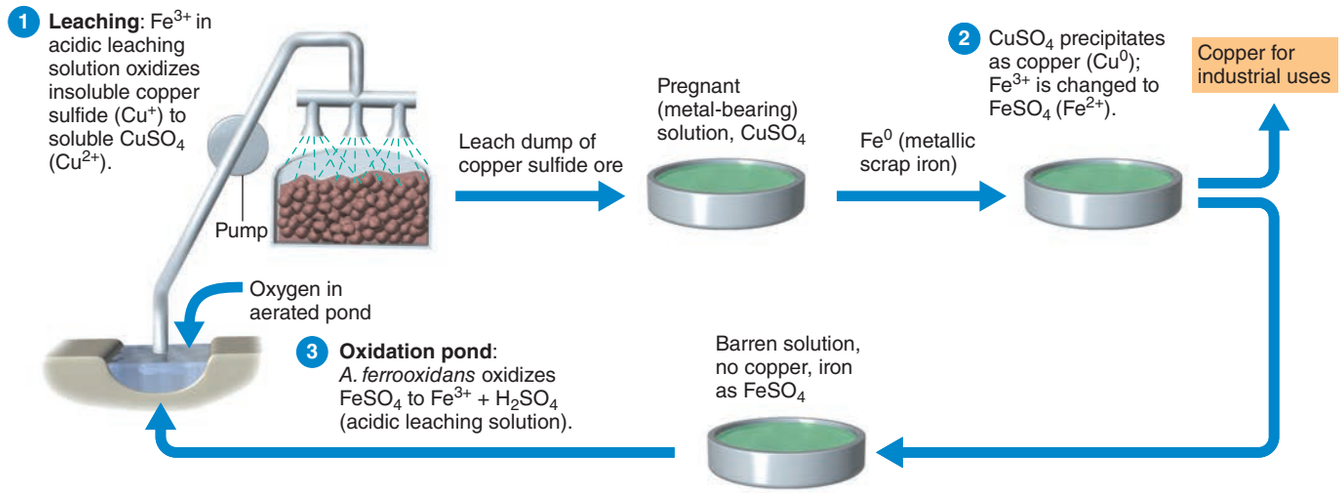


Figure 28.10 Biological leaching of copper ores. The chemistry of the process is much more complicated than shown here. Essentially, *Acidithiobacillus ferrooxidans* bacteria are used in a biological/chemical process that changes insoluble copper in the ore into soluble copper that leaches out and is precipitated as metallic copper. The solutions are continuously recirculated.

Q Name another metal that is recovered by a similar process.

ferrous iron, Fe^{2+}, and *A. ferrooxidans* are normally present in the ore and continue to contribute to the reactions. The Fe^{3+} in the sprinkling water reacts with insoluble copper (Cu^{+}) in *copper sulfides* in the ore to form soluble copper (Cu^{2+}), which takes the form of *copper sulfates* ($CuSO_4$). The soluble copper sulfate moves downslope to collection tanks, where it contacts metallic scrap iron. The copper sulfates react chemically with the iron and precipitate out as metallic copper (Cu^{0}). In this reaction, the metallic iron (Fe^{0}) is converted into ferrous iron (Fe^{2+}) that is recycled to an aerated oxidation pond, where *Acidithiobacillus* bacteria use it for energy to renew the cycle.

Microorganisms as Industrial Products

Microorganisms themselves sometimes constitute an industrial product. *Baker's yeast (S. cerevisiae)* is produced in large aerated fermentation tanks. At the end of the fermentation, the contents of the tank are about 4% yeast solids. The cells are harvested by continuous centrifuges and are pressed into the familiar yeast cakes or packets sold for home baking. Wholesale bakers purchase yeast in 50-lb boxes.

Other important microbes that are sold industrially are the symbiotic nitrogen-fixing bacteria *Rhizobium* and *Bradyrhizobium*. These organisms are usually mixed with peat moss to preserve moisture; the farmer mixes the peat moss and bacterial inoculum with the seeds of legumes to ensure infection of the plants with efficient nitrogen-fixing strains (see Chapter 27). For many years, gardeners have used the insect pathogen *Bacillus thuringiensis* to control leaf-eating insect larvae. This bacterium produces a toxin (Bt-toxin) that kills certain moths, beetles, and flies when ingested by their larvae. *B. thuringiensis* subspecies *israelensis* produces Bt-toxin that is especially active against mosquito larvae and is widely used in municipal control programs. Commercial preparations containing Bt-toxin and endospores of *B. thuringiensis* are available at almost any gardening supply store. For an example of microbes being developed to detect chemicals, see the Applications of Microbiology box on page 783.

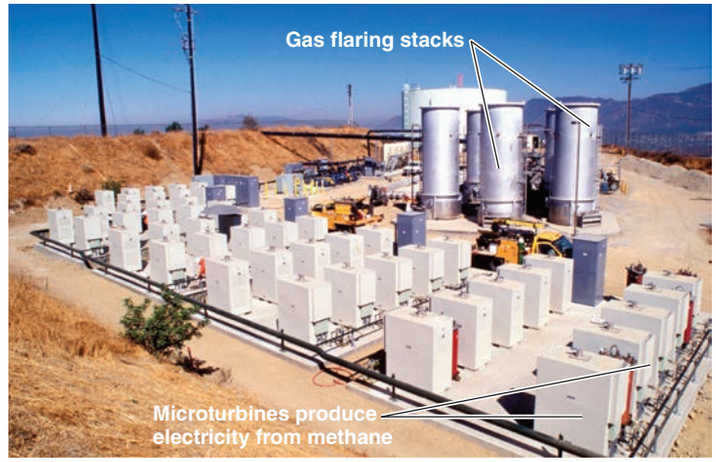


Figure 28.11 Methane production from solid wastes in landfills. Methane accumulates in landfills and can be used for energy. This installation near Los Angeles has 50 microturbines that produce electricity from methane produced by the landfill. Immediately behind the microturbines are five gas flaring stacks that mask the flames from excess flared methane—a requirement so that aircraft will not confuse it with airport lighting.

Q How is methane produced in a landfill?

CHECK YOUR UNDERSTANDING

✓ At one time, citric acid was extracted on an industrial scale from lemons and other citrus fruits. What organism is used to produce it today? **28-6**

Alternative Energy Sources Using Microorganisms

As our supplies of fossil fuels diminish or become more expensive, interest in the use of renewable energy resources will increase. Prominent among these is **biomass,** the collective organic matter produced by living organisms, including crops, trees, and municipal wastes. Microbes can be used for **bioconversion,** the process of converting biomass into alternative energy sources. Bioconversion can also decrease the amount of waste materials requiring disposal.

Methane is one of the most convenient energy sources produced from bioconversion. Many communities produce useful amounts of methane from wastes in landfill sites (**Figure 28.11**).

CHECK YOUR UNDERSTANDING

✓ Landfills are the site of a major form of bioconversion—what is the product? **28-7**

Clinical Case

The beans seem to be the most likely source of the bacteria. Dr. Chang asks how the beans are harvested and stored. He is told that after harvest, cacao beans are fermented at the farm in wooden boxes that are often covered with banana leaves. He is also told there has been only one recorded incident of *Salmonella* contamination of the raw beans. Hearing this, Dr. Chang suspects that contamination must have occurred in the room at the factory where the raw beans are kept. Looking at the room, Dr. Chang spots a discolored area on an overhead pipe in the bean room. No one has noticed the leak. The quality control microbiologist swabs the discolored area, which grows *Salmonella*.

What characteristics of chocolate prevent microbial growth?

Biofuels

As the supplies of fossil petroleum-based fuels become more expensive, and sometimes uncertain, interest in renewable replacement fuels, **biofuels,** is increasing. The initial interest has focused on **ethanol,** which is already widely used as a supplement to gasoline (90% gasoline + 10% ethanol), and the technology is well established. Brazil, for example, produces large amounts of ethanol from sugarcane, about a third of its transportation fuel. Ethanol has, however, a number of deficiencies: it cannot be transported by conventional pipelines (because it absorbs water so avidly), and it has 30% less energy content than gasoline. Also, to produce ethanol from corn creates pressures on the supply and price of a valuable foodstuff.

These drawbacks have increased interest in biofuels derived from cellulosic materials, such as cornstalks, wood, and waste-paper, and from exotic nonfood plants such as jatropha, camelina, and miscanthus. In the United States there is special interest in switchgrass—which once carpeted the prairies of the Midwest. Such grasses are perennials and require little more attention than harvesting. The technology for producing ethanol from cellulose is less well known and more expensive than that from corn or sugarcane. The sugar molecules that make up cellulose may be broken apart by enzymes—in fact, genes to synthesize these enzymes have been genetically introduced into *E. coli*. *Cellulose* sources also contain significant amounts of a similar component, *hemicellulose,* which will require organisms capable of digesting it—probably genetically modified microbes. The digestibly resistant cellulosic component *lignin* could be burned to heat early steps in fermentation processing.

"Higher" alcohols such as butanol, which have longer carbon chains, and especially branched alcohols such as isobutanol and isobutyraldehyde, have advantages over conventional ethanol. They have less capacity to absorb water and have a higher energy content. Bacteria have been genetically modified to produce several forms of higher alcohols from glucose. A basic problem in microbial production of biofuels is that we want the microbe to excrete fuel so that we eliminate the expensive step of harvesting them periodically.

A theoretically attractive organism for producing biofuels is algae. Algae offer a number of advantages; for one, they do not take up valuable farmland needed for food production. Also, algae produce 40 times the energy per acre that corn produces—and the land the algae grow on can be agriculturally nonproductive as long as it has abundant sunlight. Experimental algal production sites have even used the carbon dioxide emissions from power plants to accelerate growth. The algae can be harvested on an almost daily basis. Oils squeezed from them can be turned into biodiesel fuel and possibly jet fuel: typical algae yield 20% of their weight in oil, and some even more. After oil extraction, the remainder, rich in carbohydrates and proteins, can be used to produce ethanol or as animal feed.

Hydrogen is an attractive candidate as a replacement for fossil fuels, especially if it can be produced by splitting water. It can be used in fuel cells to generate electricity and, if burned to generate energy, does not produce harmful residues. Most research into the production of hydrogen has concentrated on physical and chemical methods, but it is also potentially possible to use bacteria or algae to produce hydrogen from the fermentation of various waste products or by modifications of photosynthesis.

The technologies outlined above will require time to reach their potential. Currently, science is in the early phases of the learning curves that all new technologies face.

CHECK YOUR UNDERSTANDING

How can microbes provide fuels for cars and electricity? **28-8**

Industrial Microbiology and the Future

Microbes have always been exceedingly useful to humankind, even when their existence was unknown. They will remain an essential part of many basic food-processing technologies. The development of recombinant DNA technology has further intensified interest in industrial microbiology by expanding the potential for new products and applications (see the Applications of Microbiology box in Chapter 1, page 3). As the supplies of fossil energy become more scarce, interest in renewable energy sources, such as hydrogen and ethanol, will increase. The use of specialized microbes to produce such products on an industrial scale will probably become more important. As new biotechnology applications and products enter the marketplace, they will affect our lives and well-being in ways that we can only speculate about today.

Clinical Case Resolved

The low moisture, high fat, and high sugar content of chocolate does not favor bacterial growth, but it does significantly increase the heat resistance of bacteria. Consequently, bacteria may survive roasting.

To address the risk posed by *Salmonella,* all food safety agencies have pursued an ongoing strategy to reduce the prevalence of the pathogen in the food chain. However, despite all the efforts, the number of salmonellosis cases remains high.

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Food Microbiology (pp. 795–801)

1. The earliest methods of preserving foods were drying, the addition of salt or sugar, and fermentation.

Foods and Disease (p. 795)

2. Food safety is monitored by the FDA and USDA and also by use of the HACCP system.

Industrial Food Canning (pp. 795–797)

3. Commercial sterilization of food is accomplished by steam under pressure in a retort.
4. Commercial sterilization heats canned foods to the minimum temperature necessary to destroy *Clostridium botulinum* endospores while minimizing alteration of the food.
5. The commercial sterilization process uses sufficient heat to reduce a population of *C. botulinum* by 12 logarithmic cycles (12D treatment).
6. Endospores of thermophiles can survive commercial sterilization.
7. Canned foods stored above 45°C can be spoiled by thermophilic anaerobes.
8. Thermophilic anaerobic spoilage is sometimes accompanied by gas production; if no gas is formed, the spoilage is called flat sour spoilage.
9. Spoilage by mesophilic bacteria is usually from improper heating procedures or leakage.
10. Acidic foods can be preserved by heat of 100°C because microorganisms that survive are not capable of growth in a low pH.
11. *Byssochlamys, Aspergillus,* and *Bacillus coagulans* are acid-tolerant and heat-resistant microbes that can spoil acidic foods.

Aseptic Packaging (p. 797)

12. Presterilized materials are assembled into packages and aseptically filled with heat-sterilized liquid foods.

Radiation and Industrial Food Preservation (pp. 797–798)

13. Gamma and X-ray radiation can be used to sterilize food, kill insects and parasitic worms, and prevent the sprouting of fruits and vegetables.

High-Pressure Food Preservation (p. 798)

14. Pressurized water is used to kill bacteria in fruit and meat.

The Role of Microorganisms in Food Production (pp. 798–801)

15. The milk protein casein curdles because of the action by lactic acid bacteria or the enzyme rennin.
16. Old-fashioned buttermilk was produced by lactic acid bacteria growing during the butter-making process.
17. Sugars in bread dough are fermented by yeast to ethanol and CO_2; the CO_2 causes the bread to rise.
18. Carbohydrates obtained from grains, potatoes, or molasses are fermented by yeasts to produce ethanol in the production of beer, ale, sake, and distilled spirits.

Industrial Microbiology (pp. 801–807)

1. Microorganisms produce alcohols and acetone that are used in industrial processes.
2. Industrial microbiology has been revolutionized by the ability of genetically modified cells to make many new products.
3. Biotechnology is a way of making commercial products by using living organisms.

Fermentation Technology (pp. 802–803)

4. The growth of cells on a large scale is called industrial fermentation.
5. Industrial fermentation is carried on in bioreactors, which control aeration, pH, and temperature.
6. Primary metabolites such as ethanol are formed as the cells grow (during the trophophase).
7. Secondary metabolites such as penicillin are produced during the stationary phase (idiophase).
8. Mutant strains that produce a desired product can be selected.
9. Enzymes or whole cells can be bound to solid spheres or fibers. When substrate passes over the surface, enzymatic reactions change the substrate to the desired product.

Industrial Products (pp. 803–806)

10. Most amino acids used in foods and medicine are produced by bacteria.
11. Microbial production of amino acids can be used to produce L-isomers; chemical production results in both D- and L-isomers.
12. Citric acid, used in foods, is produced by *Aspergillus niger.*
13. Enzymes used in manufacturing foods, medicines, and other goods are produced by microbes.
14. Some vitamins used as food supplements are made by microorganisms.
15. Vaccines, antibiotics, and steroids are products of microbial growth.
16. The metabolic activities of *Acidithiobacillus ferrooxidans* can be used to recover uranium and copper ores.
17. Yeasts are grown for wine- and breadmaking; other microbes (*Rhizobium, Bradyrhizobium,* and *Bacillus thuringiensis*) are grown for agricultural use.

Alternative Energy Sources Using Microorganisms (p. 806)

18. Organic waste, called biomass, can be converted by microorganisms into the alternative fuel methane, a process called bioconversion.
19. Fuels produced by microbial fermentation are methane, ethanol, and hydrogen.

Biofuels (p. 807)

20. Biofuels include alcohols and hydrogen (from microbial fermentation) and oils (from algae).

Industrial Microbiology and the Future (p. 807)

21. Recombinant DNA technology will continue to enhance the ability of industrial microbiology to produce medicines and other useful products.

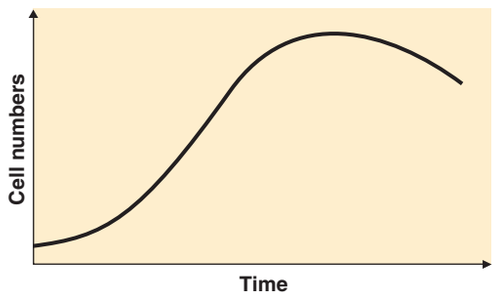
Study Questions

For answers to the Knowledge and Comprehension questions, turn to the Answers tab at the back of the textbook.

Knowledge and Comprehension

Review

1. What is industrial microbiology? Why is it important?
2. How does commercial sterilization differ from sterilization procedures used in a hospital or laboratory?
3. Why is a can of blackberries preserved by commercial sterilization typically heated to 100°C instead of at least 116°C?
4. Outline the steps in the production of cheese, and compare the production of hard and soft cheeses.
5. Beer is made with water, malt, and yeast; hops are added for flavor. What is the purpose of the water, malt, and yeast? What is malt?
6. Why is a bioreactor better than a large flask for industrial production of an antibiotic?
7. The manufacture of paper includes the use of bleach and formaldehyde-based glue. The microbial enzyme xylanase whitens paper by digesting dark lignins. Oxidase causes the fibers to stick together, and cellulase will remove ink. List three advantages of using these microbial enzymes over traditional chemical methods for making paper.
8. Describe an example of bioconversion. What metabolic processes can result in fuels?
9. DRAW IT Label the trophophase and idiophase in this graph. Indicate when primary and secondary metabolites are formed.



10. NAME IT Van Leeuwenhoek was the first to see this budding microbe, with a nucleus and cell wall; although humans have used it since before the beginning of recorded history, Louis Pasteur was the first to figure out what it does.

Multiple Choice

1. Foods packed in plastic for microwaving are
   a. dehydrated.
   b. freeze-dried.
   c. packaged aseptically.
   d. commercially sterilized.
   e. autoclaved.
2. *Acetobacter* is necessary for only one of the steps of vitamin C manufacture. The easiest way to accomplish this step would be to
   a. add substrate and *Acetobacter* to a test tube.
   b. affix *Acetobacter* to a surface and run substrate over it.
   c. add substrate and *Acetobacter* to a bioreactor.
   d. find an alternative to this step.
   e. none of the above

Use the following choices to answer questions 3–5:

a. *Bacillus coagulans*
b. *Byssochlamys*
c. flat sour spoilage
d. *Lactobacillus*
e. thermophilic anaerobic spoilage

3. The spoilage of canned foods due to inadequate processing, accompanied by gas production.
4. The spoilage of canned foods caused by *Geobacillus stearothermophilus.*
5. A heat-resistant fungus that causes spoilage in acidic foods.
6. The term *12D treatment* refers to
   a. heat treatment sufficient to kill 12 bacteria.
   b. the use of 12 different treatments to preserve food.
   c. a 10^{12} reduction in *C. botulinum* endospores.
   d. any process that destroys thermophilic bacteria.
7. Which one of the following is *not* a fuel produced by microorganisms?
   a. algal oil
   b. ethanol
   c. hydrogen
   d. methane
   e. uranium
8. Which type of radiation is used to preserve foods?
   a. ionizing
   b. nonionizing
   c. radiowaves
   d. microwaves
   e. all of the above
9. Which of the following reactions is undesirable in winemaking?
   a. Sucrose → ethanol
   b. Ethanol → acetic acid
   c. Malic acid → lactic acid
   d. Glucose → pyruvic acid
10. Which of the following reactions is an oxidation carried out by *Acidithiobacillus ferrooxidans*?
    a. $Fe^{2+} \rightarrow Fe^{3+}$
    b. $Fe^{3+} \rightarrow Fe^{2+}$
    c. $CuS \rightarrow CuSO_4$
    d. $Fe^{0} \rightarrow Cu^{0}$
    e. none of the above

Analysis

1. Which bacteria seem to be most frequently used in the production of food? Propose an explanation for this.
2. *Methylophilus methylotrophus* can convert methane (CH_4) into proteins. Amino acids are represented by this structure:

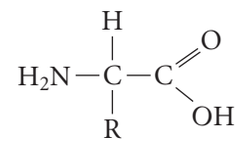
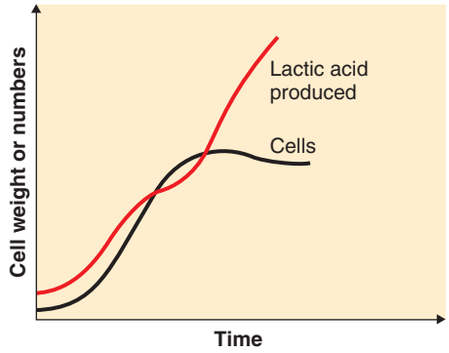


   Diagram a pathway illustrating the production of at least one amino acid.
3. Faded, worn-look denim is produced with cellulase. How does cellulase accomplish the look and feel of scores of washings? What is the source of the cellulase?

Clinical Applications and Evaluation

1. Suppose you are culturing a microorganism that produces enough lactic acid to kill itself in a few days.
   a. How can the use of a bioreactor help you maintain the culture for weeks or months? The graph below shows conditions in the bioreactor:



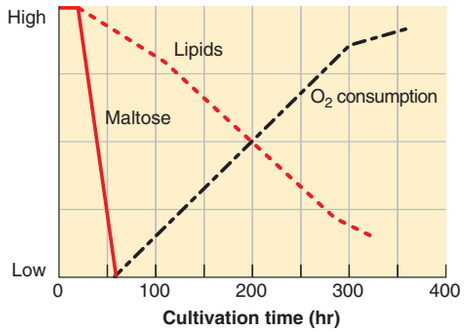
   b. If your desired product is a secondary metabolite, when can you begin collecting it?
   c. If your desired product is the cells themselves and you want to maintain a continuous culture, when can you begin harvesting?

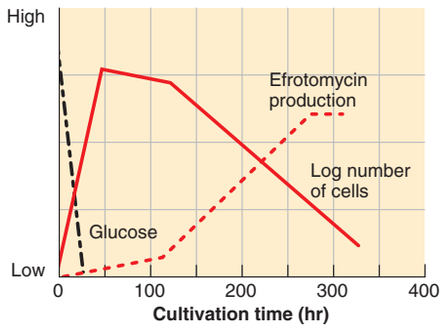
2. Researchers at the CDC inoculated apple cider with 10^5 *E. coli* O157:H7 cells/ml to determine the fate of the bacteria in apple cider (pH 3.7). They obtained the following results:

	Number of *E. coli* O157:H7 cells/ml after 25 days
Apple cider at 25°C	10^4 (mold growth evident by 10 days)
Apple cider with potassium sorbate at 25°C	10^3
Apple cider at 8°C	10^2

   What conclusions can you reach from these data? What disease is caused by *E. coli* O157:H7? (*Hint:* See Chapter 25.)

3. The antibiotic efrotomycin is produced by *Streptomyces lactamdurans. S. lactamdurans* was grown in 40,000 liters of medium. The medium consisted of glucose, maltose, soybean oil, $(NH_4)_2SO_4$, NaCl, KH_2PO_4, and Na_2HPO_4. The culture was aerated and maintained at 28°C. The following results were obtained from analyses of the culture medium during cell growth:





   a. Under what conditions is the most efrotomycin produced? Is it a primary or secondary metabolite?
   b. Which is used first, maltose or glucose? Suggest a reason for this.
   c. What is the purpose of each ingredient in the growth medium? (*Hint:* See Chapter 6.)
   d. What is *Streptomyces*? (*Hint:* See Chapter 11.)

Answers to Knowledge and Comprehension Study Questions

Chapter 1

Review

1. People came to believe that living organisms arise from nonliving matter because they would see flies coming out of manure, maggots coming out of dead animals, and microorganisms appearing in liquids after a day or two.

2. **a.** Certain microorganisms cause diseases in insects. Microorganisms that kill insects can be effective biological control agents because they are specific for the pest and do not persist in the environment.
   b. Carbon, oxygen, nitrogen, sulfur, and phosphorus are required for all living organisms. Microorganisms convert these elements into forms that are useful for other organisms. Many bacteria decompose material and release carbon dioxide into the atmosphere, which plants use. Some bacteria can take nitrogen from the atmosphere and convert it into a form that plants and other microorganisms can use.
   c. Normal microbiota are microorganisms that are found in and on the human body. They do not usually cause disease and can be beneficial.
   d. Organic matter in sewage is decomposed by bacteria into carbon dioxide, nitrates, phosphates, sulfate, and other inorganic compounds in a wastewater treatment plant.
   e. Recombinant DNA techniques have resulted in insertion of the gene for insulin production into bacteria. These bacteria can produce human insulin inexpensively.
   f. Microorganisms can be used as vaccines. Some microbes can be genetically modified to produce components of vaccines.
   g. Biofilms are aggregated bacteria adhering to each other and to a solid surface.

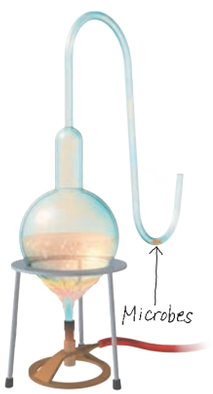
3. **a.** 1, 3 **c.** 1, 4, 5 **e.** 5 **g.** 4
   b. 8 **d.** 2 **f.** 3 **h.** 7

4. **a.** 7 **c.** 3 **e.** 6 **g.** 1
   b. 4 **d.** 2 **f.** 5

5. **a.** 11 **e.** 3 **i.** 1 **m.** 7 **q.** 13
   b. 14 **f.** 9 **j.** 12 **n.** 5 **r.** 16
   c. 15 **g.** 10 **k.** 18 **o.** 6
   d. 17 **h.** 2 **l.** 4 **p.** 8

6. **a.** *B. thuringiensis* is sold as a biological insecticide.
   b. *Saccharomyces* is the yeast sold for making bread, wine, and beer.

7. Bacteria

8. 

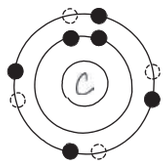
Multiple Choice

1. a
2. c
3. d
4. c
5. b
6. e
7. c
8. a
9. c
10. a

Chapter 2

Review

1. Atoms with the same atomic number and chemical behavior are classified as chemical elements.

2. 

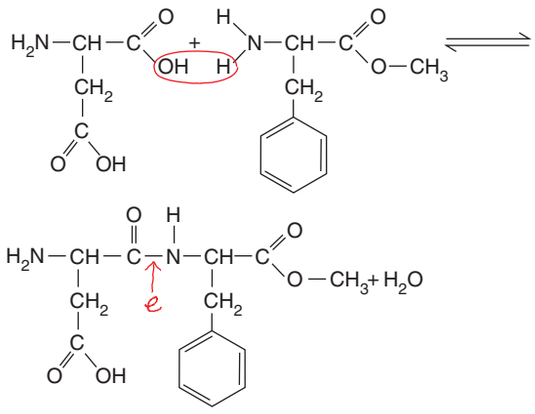
3. **a.** Ionic
   b. Single covalent bond
   c. Double covalent bonds
   d. Hydrogen bond

4. **a.** Synthesis reaction, condensation, or dehydration
   b. Decomposition reaction, digestion, or hydrolysis
   c. Exchange reaction
   d. Reversible reaction

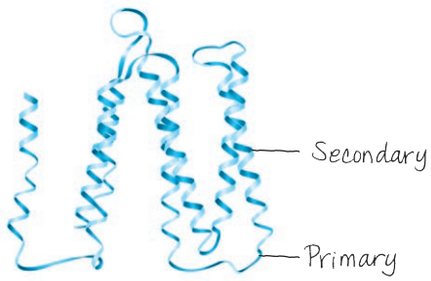
5. The enzyme lowers the activation energy required for the reaction and therefore speeds up this decomposition reaction.

6. **a.** Lipid
   b. Protein
   c. Carbohydrate
   d. Nucleic acid

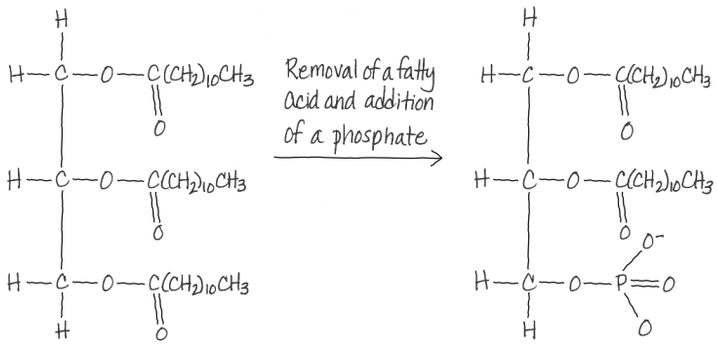
7. **a.** Amino acids
   b. Right to left
   c. Left to right



8. The entire protein shows tertiary structure, held by disulfide bonds. No quaternary structure.



9.



10. Fungus

Multiple Choice

1. c	**3.** b	**5.** b	**7.** a	**9.** b
2. b	**4.** e	**6.** c	**8.** a	**10.** c

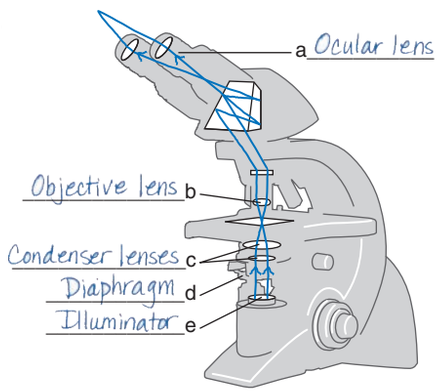
Chapter 3

Review

1. a. 10^{26} m; **b.** 1nm; **c.** 10^3 nm

2. a. Compound light microscope
b. Darkfield microscope
c. Phase-contrast microscope
d. Fluorescence microscope
e. Electron microscope
f. Differential interference contrast microscope

3.



4.

Ocular Lens Magnification	×	Oil Immersion Lens Magnification	=	Total Magnification of Specimen
10×		100×		1000×

5. a. 2,000×
b. 100,000×
c. 0.2 μm
d. 0.0025 μm
e. Seeing three-dimensional detail.

6. In a Gram stain, the mordant combines with the basic dye to form a complex that will not wash out of gram-positive cells. In a flagella stain, the mordant accumulates on the flagella so that they can be seen with a light microscope.

7. A counterstain stains the colorless non–acid-fast cells so that they are easily seen through a microscope.

8. In the Gram stain, the decolorizer removes the color from gram-negative cells. In the acid-fast stain, the decolorizer removes the color from non–acid-fast cells.

9. a. Purple **e.** Purple
b. Purple **f.** Purple
c. Purple **g.** Colorless
d. Purple **h.** Red

10. An acid-fast bacterium *(Mycobacterium)*

Multiple Choice

1. c	**3.** b	**5.** a	**7.** d	**9.** a
2. d	**4.** a	**6.** e	**8.** b	**10.** c

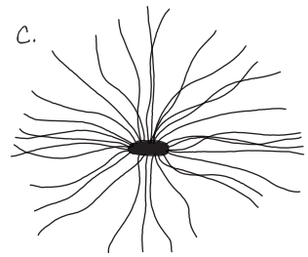
Chapter 4

Review

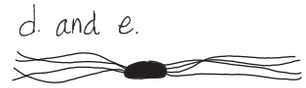
1. a. and e. b. and e.



c.

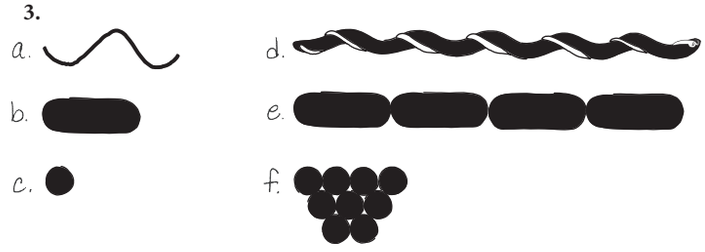


d. and e.



2. a. sporogenesis
b. certain adverse environmental conditions
c. germination
d. favorable growth conditions

3.



4. **a.** 4
   b. 6
   c. 1
   d. 3
   e. 1, 5
   f. 3, 9
   g. 2, 8
   h. 7

5. An endospore is called a resting structure because it provides a method for one cell to "rest," or survive, as opposed to grow and reproduce. The protective endospore wall allows a bacterium to withstand adverse conditions in the environment.

6. **a.** Both allow materials to cross the plasma membrane from a high concentration to a low concentration without expending energy. Facilitated diffusion requires carrier proteins.
   b. Both require enzymes to move materials across the plasma membrane. In active transport, energy is expended.
   c. Both move materials across the plasma membrane with an expenditure of energy. In group translocation, the substrate is changed after it crosses the membrane.

7. **a.** Diagram (a) refers to a gram-positive bacterium because the lipopolysaccharide–phospholipid–lipoprotein layer is absent.
   b. The gram-negative bacterium initially retains the violet stain, but it is released when the outer membrane is dissolved by the decolorizing agent. After the dye–iodine complex enters, it becomes trapped by the peptidoglycan of gram-positive cells.
   c. The outer layer of the gram-negative cells prevents penicillin from entering the cells.
   d. Essential molecules diffuse through the gram-positive wall. Porins and specific channel proteins in the gram-negative outer membrane allow passage of small water-soluble molecules.
   e. Gram-negative.

8. An extracellular enzyme (amylase) hydrolyzes starch into disaccharides (maltose) and monosaccharides (glucose). A carrier enzyme (maltase) hydrolyzes maltose and moves one glucose into the cell. Glucose can be transported by group translocation as glucose-6-phosphate.

9. **a.** 3
   b. 4
   c. 7
   d. 1
   e. 6
   f. 2
   g. 5

10. Actinomycete

Multiple Choice

1. e	**3.** b	**5.** d	**7.** b	**9.** a
2. d	**4.** a	**6.** e	**8.** e	**10.** b

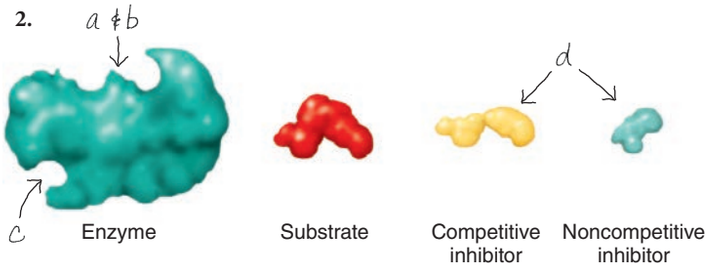
Chapter 5

Review

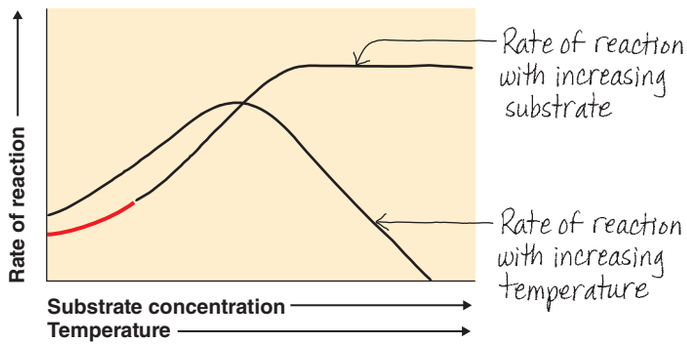
1. **(a)** is the Calvin-Benson cycle, **(b)** is glycolysis, and **(c)** is the Krebs cycle.
   a. Glycerol is catabolized by pathway (b) as dihydroxyacetone phosphate. Fatty acids by pathway (c) as acetyl groups.
   b. In pathway (c) at α-ketoglutaric acid.
   c. Glyceraldehyde-3-phosphate from the Calvin-Benson cycle enters glycolysis. Pyruvic acid from glycolysis is decarboxylated to produce acetyl for the Krebs cycle.
   d. In (a), between glucose and glyceraldehyde-3-phosphate.
   e. The conversion of pyruvic acid to acetyl, isocitric acid to α-ketoglutaric acid, and α-ketoglutaric acid to succinyl~CoA.
   f. By pathway (c) as acetyl groups.
   g.

	Uses	Produces
Calvin-Benson cycle	6 NADPH	
Glycolysis		2 NADH
Pyruvic acid → acetyl		1 NADH
Isocitric acid → α-ketoglutaric acid		1 NADH
α-ketoglutaric acid → Succinyl~CoA		1 NADH
Succinic acid → Fumaric acid		1 $FADH_2$
Malic acid → Oxaloacetic acid		1 NADH

   h. Dihydroxyacetone phosphate; acetyl; oxaloacetic acid; α-ketoglutaric acid.

2. 

e. When the enzyme and substrate combine, the substrate molecule will be transformed.
When the competitive inhibitor binds to the enzyme, the enzyme will not be able to bind with the substrate.
When the noncompetitive inhibitor binds to the enzyme, the active site of the enzyme will be changed so the enzyme cannot bind with the substrate.

3. 

4. Oxidation-reduction: A coupled reaction in which one substance loses electrons and another gains electrons.
   a. The final electron acceptor in aerobic respiration is molecular oxygen; in anaerobic respiration, it is another inorganic molecule.
   b. An electron transport chain is used in respiration but not in fermentation. The final electron acceptor in respiration is usually inorganic; in fermentation it is usually organic.
   c. In cyclic photophosphorylation, electrons are returned to chlorophyll. In noncyclic photophosphorylation, chlorophyll receives electrons from hydrogen atoms.

5. **a.** Photophosphorylation
   b. Oxidative phosphorylation
   c. Substrate-level phosphorylation

6. oxidation

7. **a.** CO_2
   b. Light
   c. Organic molecules
   d. Light
   e. CO_2
   f. Inorganic molecules
   g. Organic molecules
   h. Organic molecules

8. Protons are pumped from one side of the membrane to the other; transfer of protons back across the membrane generates ATP.
   a and **b.** Outer portion is acidic and has a positive electrical charge.
   c. Energy-conserving sites are the three loci where protons are pumped out. **d.** Kinetic energy is realized at ATP synthase

9. NAD^+ is needed to pick up more electrons. NADH is usually reoxidized in respiration. NADH can be reoxidized in fermentation.

10. Chemoautotroph

Multiple Choice

1. a	**3.** b	**5.** c	**7.** b	**9.** c
2. d	**4.** c	**6.** b	**8.** a	**10.** b

Chapter 6

Review

1. In binary fission, the cell elongates, and the chromosome replicates. Next, the nuclear material is evenly divided. The plasma membrane invaginates toward the center of the cell. The cell wall thickens and grows inward between the membrane invaginations; two new cells results.

2. Carbon: synthesis of molecules that make up a living cell. **H**ydrogen: source of electrons and component of organic molecules. **O**xygen: component of organic molecules; electron acceptor in aerobes. **N**itrogen: component of amino acids. **P**hosphorus: in phospholipids and nucleic acids. **S**ulfur: In some amino acids.

3. **a.** Catalyzes the breakdown of H_2O_2 to O_2 and H_2O.
   b. H_2O_2; peroxide ion is O_2^{2-}.
   c. Catalyzes the breakdown of H_2O_2;

$$NADH + H^+ + H_2O_2 \xrightarrow{\text{Peroxidase}} NAD^+ + 2H_2O$$

   d. O_2^-; this anion has one unpaired electron.
   e. Converts superoxide to O_2 and H_2O_2;

$$2O_2^- + 2H^+ \xrightarrow{\text{Superoxide dismutase}} O_2 + H_2O_2$$

   The enzymes are important in protecting the cell from the strong oxidizing agents, peroxide and superoxide, that form during respiration.

4. Direct methods are those in which the microorganisms are seen and counted. Direct methods are direct microscopic count, plate count, filtration, and most probable number.

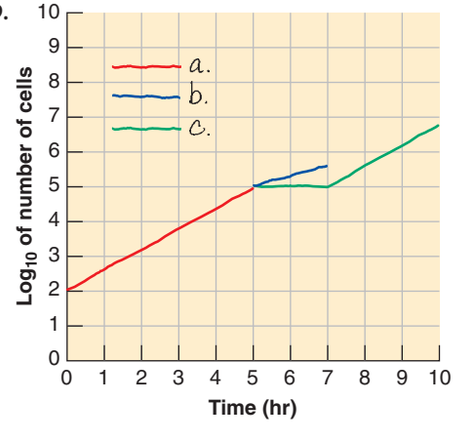
5. The growth rate of bacteria slows down with decreasing temperatures. Mesophilic bacteria will grow slowly at refrigeration temperatures and will remain dormant in a freezer. Bacteria will not spoil food quickly in a refrigerator.

6. Number of cells $\times$ $2^{\text{n generations}}$ = Total number of cells

$$6 \quad \times \quad 2^7 \quad = \quad 768$$

7. Petroleum can meet the carbon and energy requirements for an oil-degrading bacterium; however, nitrogen and phosphate are usually not available in large quantities. Nitrogen and phosphate are essential for making proteins, phospholipids, nucleic acids, and ATP.

8. A chemically defined medium is one in which the exact chemical composition is known. A complex medium is one in which the exact chemical composition is not known.

9. 

10. Cold, salty, aerobic

Multiple Choice

1. c	**3.** c	**5.** c	**7.** e	**9.** b
2. a	**4.** a	**6.** d	**8.** c	**10.** b

Chapter 7

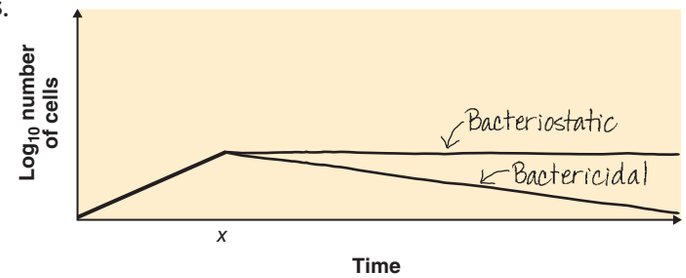
Review

1. Autoclave. Because of the high specific heat of water, moist heat is readily transferred to cells.

2. Pasteurization destroys most organisms that cause disease or rapid spoilage of food.

3. Variables that affect determination of the thermal death point are
   - The innate heat resistance of the strain of bacteria
   - The past history of the culture, whether it was freeze-dried, wetted, etc.
   - The clumping of the cells during the test
   - The amount of water present
   - The organic matter present
   - Media and incubation temperature used to determine viability of the culture after heating

4. **a.** the ability of ionizing radiation to break DNA directly. However, because of the high water content of cells, free radicals (H · and OH ·) that break DNA strands are likely to form.
   b. formation of thymine dimers.

5. 

6. All three processes kill microorganisms; however, as moisture and/or temperatures are increased, less time is required to achieve the same result.

7. Salts and sugars create a hypertonic environment. Salts and sugars (as preservatives) do not directly affect cell structures or metabolism; instead, they alter the osmotic pressure. Jams and jellies are preserved with sugar; meats are usually preserved with salt. Molds are more capable of growth in high osmotic pressure than are bacteria.

8. Disinfectant B is preferable because it can be diluted more and still be effective.

9. Quaternary ammonium compounds are most effective against gram-positive bacteria. Gram-negative bacteria that were stuck in cracks or around the drain of the tub would not have been washed away when the tub was cleaned. These gram-negative bacteria could survive the washing procedure. Some pseudomonads can grow on quats that have accumulated.

10. Pseudomonads (*Pseudomonas* and *Burkholderia*)

Multiple Choice

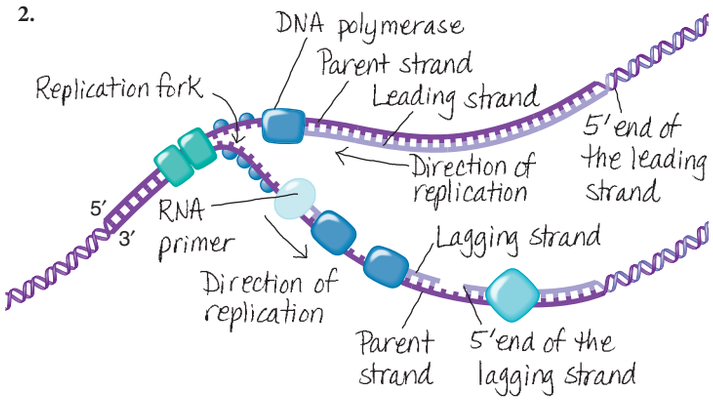
1. d	**3.** d	**5.** a	**7.** b	**9.** b
2. b	**4.** d	**6.** a	**8.** b	**10.** b

Chapter 8

Review

1. DNA consists of a strand of alternating sugars (deoxyribose) and phosphate groups with a nitrogenous base attached to each sugar. The bases are adenine, thymine, cytosine, and guanine. DNA exists in a cell as two strands twisted together to form a double helix. The two strands are held together by hydrogen bonds between their nitrogenous bases. The bases are paired in a specific, complementary way: A-T and C-G. The information held in the sequence of nucleotides in DNA is the basis for synthesis of RNA and proteins in a cell.

2.



3. **a.** 2
b. 4
c. 3
d. 1
e. 5

4. **a.** ATATTACTTTGCATGGACT
b. met-lys-arg-thr-(end)
c. TATAATGAAACGTTCCTGA
d. No change
e. Cysteine substituted for arginine
f. Proline substituted for threonine (missense mutation)
g. Frameshift mutation
h. Adjacent thymines might polymerize
i. ACT

5. Iron deficiency could stimulate miRNA that is complementary to RNA encoding iron-requiring proteins.

6. **a.** After translation
b. After transcription
c. Before transcription
d. Before transcription

7. CTTTGA. Endospores and pigments offer protection against UV radiation. Additionally, repair mechanisms can remove and replace thymine polymers.

8. **a.** Culture 1 will remain the same. Culture 2 will convert to F^+ but will have its original genotype.
b. The donor and recipient cells' DNA can recombine to form combinations of $A^+B^+C^+$ and $A^-B^-C^-$. If the F plasmid also is transferred, the recipient cell may become F^+.

9. Mutation and recombination provide genetic diversity. Environmental factors select for the survival of organisms through natural selection. Genetic diversity is necessary for the survival of some organisms through the processes of natural selection. Organisms that survive may undergo further genetic change, resulting in the evolution of the species.

10. *Escherichia coli*

Multiple Choice

1. c	**3.** c	**5.** c	**7.** a	**9.** d
2. d	**4.** d	**6.** b	**8.** c	**10.** a

Chapter 9

Review

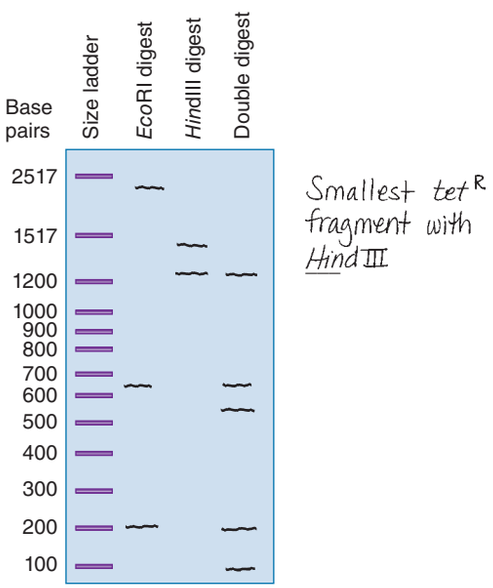
1. **a.** Both are DNA. cDNA is a segment of DNA made by RNA-dependent DNA polymerase. It is not necessarily a gene; a gene is a transcribable unit of DNA that codes for protein or RNA.
b. Both are DNA. A RFLP is a segment of DNA produced when a restriction endonuclease hydrolyzes DNA. It is not usually a gene; a gene is a transcribable unit of DNA that codes for protein or RNA.
c. Both are DNA. A DNA probe is a short, single-stranded piece of DNA. It is not a gene; a gene is a transcribable unit of DNA that codes for protein or RNA.
d. Both are enzymes. DNA polymerase synthesizes DNA one nucleotide at a time using a DNA template; DNA ligase joins pieces (strands of nucleotides) together.
e. Both are DNA. Recombinant DNA results from joining DNA from two different sources; cDNA results from copying a strand of RNA.
f. The proteome is the expression of the genome. An organism's genome is one complete copy of its genetic information. The proteins encoded by this genetic material comprise the proteome.

2. In protoplast fusion, two wall-less cells fuse together to combine their DNA. A variety of genotypes can result from this process. In b, c, and d, specific genes are inserted directly into the cell.

3. **a.** *Bam*HI, *Eco*RI, and *Hin*dIII make sticky ends.
b. Fragments of DNA produced with the same restriction enzyme will spontaneously anneal to each other at their sticky ends.

4. The gene can be spliced into a plasmid and inserted into a bacterial cell. As the cell grows, the number of plasmids will increase.
The polymerase chain reaction can make copies of a gene using DNA polymerase and a primer for the gene.

5.



6. In a eukaryotic cell, RNA polymerase copies DNA; RNA processing removes the introns, leaving the exons in the mRNA. cDNA can be made from the mRNA by reverse transcriptase.
7. See Tables 9.2 and 9.3.
8. You probably used a few plant cells in a Petri plate for your experiment. You can grow these cells on plant-cell culture media with tetracycline. Only the cells with the new plasmid will grow.
9. In RNAi, siRNA binds mRNA creating double-stranded RNA, which is enzymatically destroyed.
10. Retroviridae

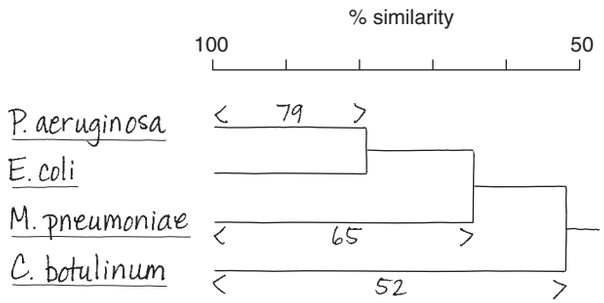
Multiple Choice

1. b	3. b	5. c	7. c	9. e
2. b	4. b	6. d	8. b	10. a

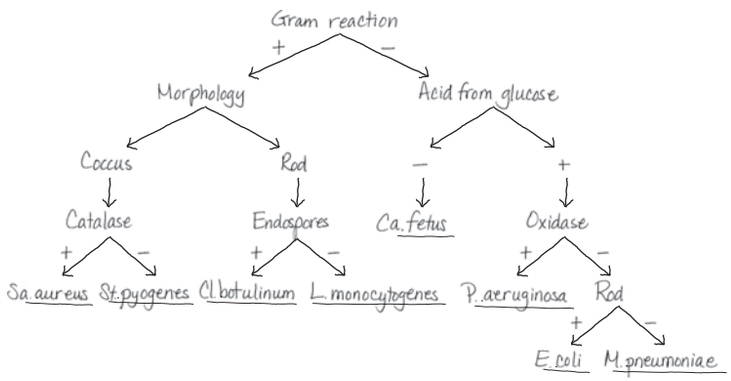
Chapter 10

Review

1. A and D appear to be most closely related because they have similar G-C moles %. No two are the same species.
2. A and D are most closely related.
3. The purpose of a cladogram is to show the degree of relatedness between organisms. A dichotomous key can be used for identification but doesn't show relatedness like the cladogram. Mycoplasma and Escherichia are on one branch in the key, but the cladogram indicates Mycoplasma is more closely related to Clostridium.



4. One possible key is shown below. Alternative keys could be made starting with morphology or glucose fermentation.



5. *Bordetella bronchiseptica*

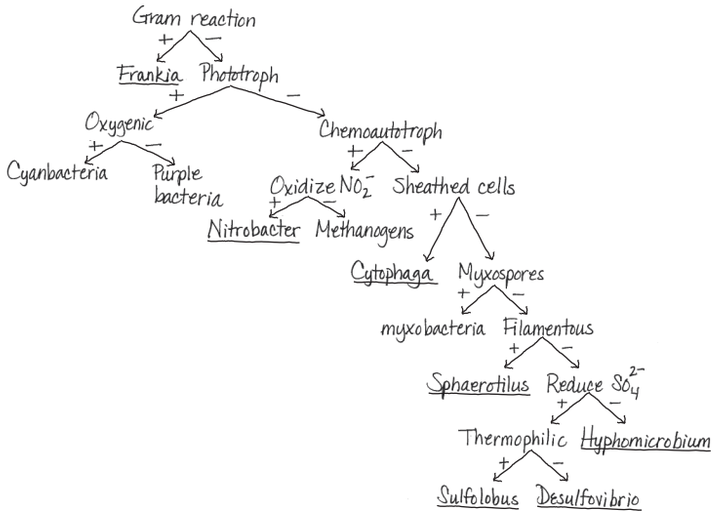
Multiple Choice

1. b	3. d	5. e	7. a	9. a
2. e	4. b	6. a	8. e	10. b

Chapter 11

Review

1. **a.** *Clostridium*
   b. *Bacillus*
   c. *Streptomyces*
   d. *Mycobacterium*
   e. *Streptococcus*
   f. *Staphylococcus*
   g. *Treponema*
   h. *Spirillum*
   i. *Pseudomonas*
   j. *Escherichia*
   k. *Mycoplasma*
   l. *Rickettsia*
   m. *Chlamydia*
2. **a.** Both are oxygenic photoautotrophs. Cyanobacteria are prokaryotes; algae are eukaryotes.
   b. Both are chemoheterotrophs capable of forming mycelia; some form conidia. Actinomycetes are prokaryotes; fungi are eukaryotes.
   c. Both are large rod-shaped bacteria. *Bacillus* forms endospores, *Lactobacillus* is a fermentative non–endospore-forming rod.
   d. Both are small rod-shaped bacteria. *Pseudomonas* has an oxidative metabolism; *Escherichia* is fermentative. *Pseudomonas* has polar flagella; *Escherichia* has peritrichous flagella.
   e. Both are helical bacteria. *Leptospira* (a spirochete) has an axial filament. *Spirillum* has flagella.
   f. Both are gram-negative, rod-shaped bacteria. *Escherichia* are facultative anaerobes, and *Bacteroides* are anaerobes.
   g. Both are obligatory intracellular parasites. *Rickettsia* are transmitted by ticks; *Chlamydia* have a unique developmental cycle.
   h. Both are atypical gram-positive bacteria. *Mycobacterium* is a high G+C, acid-fast genus. *Mycoplasma* is a low G+C genus that lacks cell walls.
3. There are many ways to draw a key. Here is one example.



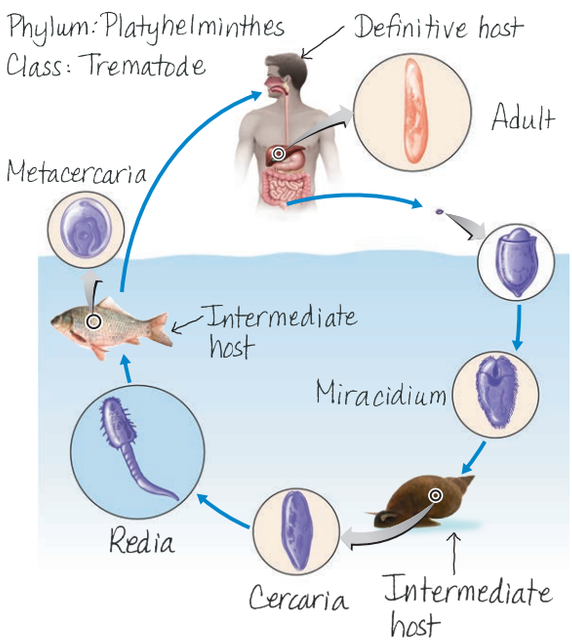
4. Methanogens

Multiple Choice

1. b	3. e	5. b	7. e	9. b
2. b	4. a	6. c	8. b	10. a

Chapter 12

Review

1. **a.** Systemic
   b. Subcutaneous
   c. Cutaneous
   d. Superficial
   e. Systemic
2. **a.** *E. coli*
   b. *P. chrysogenum*
3. Arthroconidia *(Trichophyton)*
4. As the first colonizers on newly exposed rock or soil, lichens are responsible for the chemical weathering of large inorganic particles and the consequent accumulation of soil.
5. Cellular slime molds exist as individual ameboid cells. Plasmodial slime molds are multinucleate masses of protoplasm. Both survive adverse environmental conditions by forming spores.
6. **a.** Flagella
   b. *Giardia*
   c. None
   d. *Nosema*
   e. Pseudopods
   f. *Entamoeba*
   g. None
   h. *Plasmodium*
   i. Cilia
   j. *Balantidium*
   k. Flagella
   l. *Trypanosoma*
   m. Flagella
   n. *Trichomonas*
7. *Trichomonas* cannot survive for long outside a host because it does not form a protective cyst. *Trichomonas* must be transferred from host to host quickly.
8. Ingestion
9. The male reproductive organs are in one individual, and the female reproductive organs in another. Nematodes belong to the Phylum Aschelminthes.
10. 

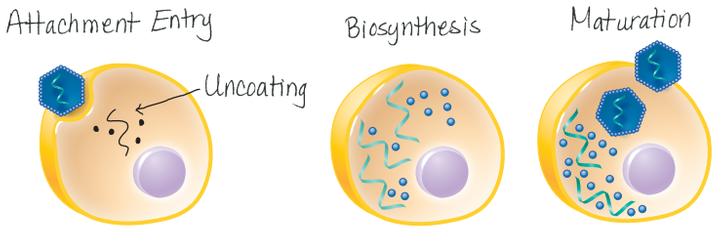
Multiple Choice

1. d	**3.** b	**5.** a	**7.** b	**9.** a
2. b	**4.** d	**6.** d	**8.** d	**10.** c

Chapter 13

Review

1. Viruses absolutely require living host cells to multiply.
2. A virus
   - contains DNA or RNA;
   - has a protein coat surrounding the nucleic acid;
   - multiplies inside a living cell using the synthetic machinery of the cell; and
   - causes the synthesis of virions.

   A virion is a fully developed virus particle that transfers the viral nucleic acid to another cell and initiates multiplication.
3. Polyhedral (Figure 13.2); helical (Figure 13.4); enveloped (Figure 13.3); complex (Figure 13.5).
4. 

5. Both produce double-stranded RNA with the − strand being the template for more + strands. + strands act as mRNA in both virus groups.
6. Antibiotic treatment of *S. aureus* can activate phage genes that encode P-V leukocidin.
7. **a.** Viruses cannot easily be observed in host tissues. Viruses cannot easily be cultured in order to be inoculated into a new host. Additionally, viruses are specific for their hosts and cells, making it difficult to substitute a laboratory animal for the third step of Koch's postulates.
   b. Some viruses can infect cells without inducing cancer. Cancer may not develop until long after infection. Cancers do not seem to be contagious.
8. **a.** subacute sclerosing panencephalitis
   b. common viruses
   c. Answers will vary. One example of a possible mechanism is latent, in an abnormal tissue.
9. **a.** of the rigid cell walls
   b. vectors such as sap-sucking insects
   c. plant protoplasts and insect cell cultures
10. Herpesviridae

Multiple Choice

1. e	**3.** b	**5.** b	**7.** c	**9.** d
2. c	**4.** c	**6.** e	**8.** d	**10.** c

Chapter 14

Review

1. **a.** Etiology is the study of the cause of a disease, whereas pathogenesis is the manner in which the disease develops.
   b. *Infection* refers to the colonization of the body by a microorganism. Disease is any change from a state of health. A disease may, but does not always, result from infection.

c. A communicable disease is a disease that is spread from one host to another, whereas a noncommunicable disease is not transmitted from one host to another.

2. *Symbiosis* refers to unlike organisms living together. Commensalism—one of the organisms benefits and the other is unaffected; e.g., corynebacteria living on the surface of the eye. Mutualism—both organisms benefit; e.g., *E. coli* receives nutrients and a constant temperature in the large intestine and produces vitamin K and certain B vitamins that are useful for the human host. Parasitism—one organism benefits while the other is harmed; e.g., *Salmonella enterica* receives nutrients and warmth in the large intestine, and the human host experiences gastroenteritis or typhoid fever.

3. **a.** Acute
b. Chronic
c. Subacute

4. Hospital patients may be in a weakened condition and therefore predisposed to infection. Pathogenic microorganisms are generally transmitted to patients by contact and airborne transmission. The reservoirs of infection are the hospital staff, visitors, and other patients.

5. Changes in body function that the patient feels are called *symptoms*. Symptoms such as weakness or pain are not measurable by a physician. Objective changes that the physician can observe and measure are called *signs*.

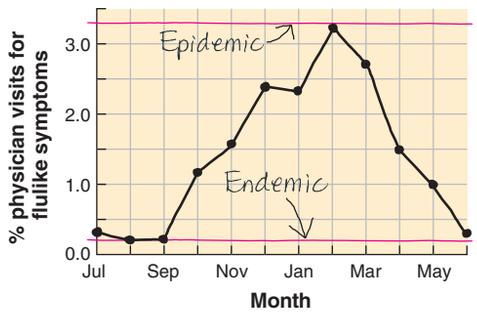
6. When microorganisms causing a local infection enter a blood or lymph vessel and are spread throughout the body, a systemic infection can result.

7. Mutualistic microorganisms are providing a chemical or environment that is essential for the host. Commensal organisms are not essential; another microorganism might serve the function as well.

8. Incubation period, prodromal period, period of illness, period of decline (may be crisis), period of convalescence.

9. *Escherichia coli*

10.



Multiple Choice

1. a **3.** a **5.** d **7.** c **9.** c
2. b **4.** d **6.** a **8.** a **10.** b

Chapter 15

Review

1. The ability of a microorganism to produce a disease is called *pathogenicity*. The degree of pathogenicity is *virulence*.

2. Encapsulated bacteria can resist phagocytosis and continue growing. *Streptococcus pneumoniae* and *Klebsiella pneumoniae* produce capsules that are related to their virulence. M protein found in the cell walls of *Streptococcus pyogenes* and A protein in the cell walls of *Staphylococcus aureus* help these bacteria resist phagocytosis.

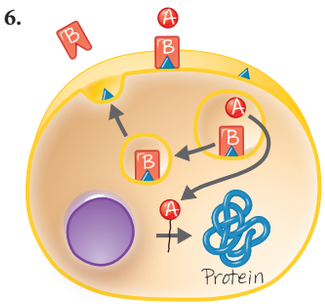
3. Hemolysins lyse red blood cells; hemolysis might supply nutrients for bacterial growth. Leukocidins destroy neutrophils and macrophages that are active in phagocytosis; this decreases host resistance to infection. Coagulase causes fibrinogen in blood to clot; the clot may protect the bacterium from phagocytosis and other host defenses. Bacterial kinases break down fibrin; kinases can destroy a clot that was made to isolate the bacteria, thus allowing the bacteria to spread. Hyaluronidase hydrolyzes the hyaluronic acid that binds cells together; this could allow the bacteria to spread through tissues. Siderophores take iron from host iron-transport proteins, thus allowing bacteria to get iron for growth. IgA proteases destroy IgA antibodies; IgA antibodies protect mucosal surfaces.

4. **a.** Would inhibit bacteria.
b. Would prevent adherence of *N. gonorrhoeae*.
c. *S. pyogenes* would not be able to attach to host cells and would be more susceptible to phagocytosis.

5.

	Exotoxin	Endotoxin
Bacterial source	Gram +	Gram −
Chemistry	Proteins	Lipid A
Toxigenicity	High	Low
Pharmacology	Destroy certain cell parts or physiological functions	Systemic, fever, weakness, aches and shock
Example	Botulinum toxin	Salmonellosis

6.



7. Pathogenic fungi do not have specific virulence factors; capsules, metabolic products, toxins, and allergic responses contribute to the virulence of pathogenic fungi. Some fungi produce toxins that, when ingested, produce disease. Protozoa and helminths elicit symptoms by destroying host tissues and producing toxic metabolic wastes.

8. *Legionella*

9. Viruses avoid the host's immune response by growing inside host cells; some can remain latent in a host cell for prolonged periods. Some protozoa avoid the immune response by mutations that change their antigens.

10. *Neisseria gonorrhoeae*

Multiple Choice

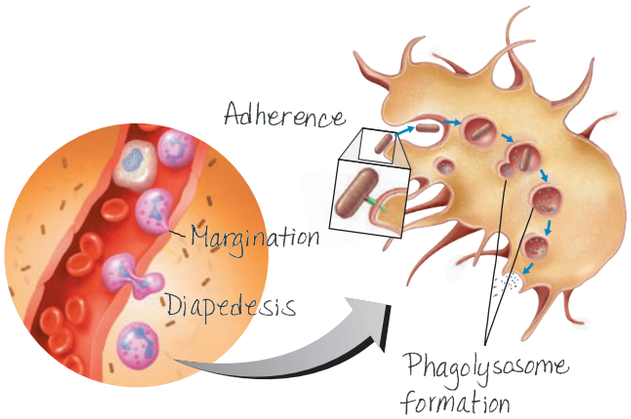
1. d **3.** d **5.** c **7.** b **9.** d
2. c **4.** a **6.** a **8.** a **10.** c

Chapter 16

Review

1. **a.** Mechanical: movement out; Chemical: lysozome; acids
b. Mechanical: movement out; Chemical: acidic environment in female

2. Inflammation is the body's response to tissue damage. The characteristic symptoms of inflammation are redness, pain, heat, and swelling.

3. Interferons are defensive proteins. Alpha interferon and beta interferon induce uninfected cells to produce antiviral proteins. Gamma interferon is produced by lymphocytes and activates neutrophils to kill bacteria.
4. Endotoxin binds C3b, which activates C5–C9 to cause cell lysis. This can result in free cell wall fragments, which bind more C3b, resulting in C5–C9 damage to host cell membranes.
5. Toxic oxygen products can kill pathogens.
6. The recipient's antibodies combine with donor antigens and fix complement; the activated complement causes hemolysis.
7. Inhibit formation of C3b; prevent MAC formation; hydrolyze C5a.
8. 

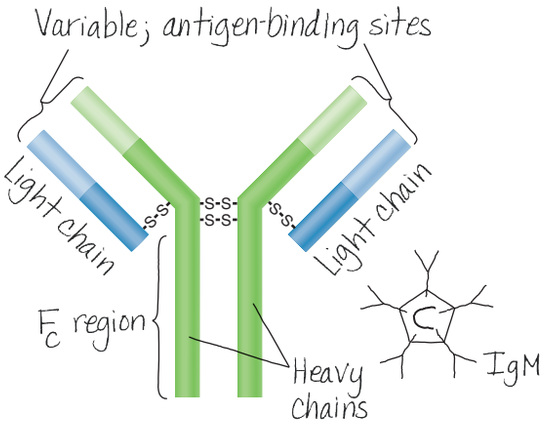
9. **a.** Innate. Facilitate adherence of phagocyte and pathogen.
   b. Innate. Bind iron.
   c. Innate. Kill or inhibit bacteria.
10. Monocyte (macrophage)

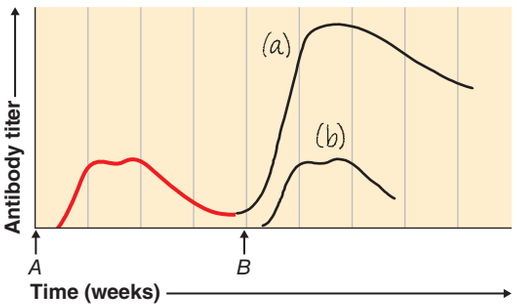
Multiple Choice

1. a	3. c	5. e	7. c	9. d
2. d	4. d	6. a	8. b	10. e

Chapter 17

Review

1. **a.** Adaptive immunity is the resistance to infection obtained during the life of the individual; it results from the production of antibodies and T cells. Innate immunity refers to the resistance of species or individuals to certain diseases that is not dependent on antigen-specific immunity.
   b. Humoral immunity is due to antibodies (and B cells). Cellular immunity is due to T cells.
   c. Active immunity refers to antibodies produced by the individual who carries them. Passive immunity refers to antibodies produced by another source and then transferred to the individual who needs the antibodies.
   d. T_H1 cells produce cytokines that activate T cells. Cytokines produced by T_H2 cells activate B cells.
   e. Natural immunity is acquired naturally, i.e., from mother to newborn, or following an infection. Artificial immunity is acquired from medical treatment, i.e., by injection of antibodies or by vaccination.
   f. T-dependent antigens: Certain antigens must combine with self-antigens to be recognized by T_H cells and then by B cells. T-independent antigens can elicit an antibody response without T cells.
   g. T cells can be classified by their surface antigens: T_H cells possess the CD4 antigen; T_C cells have the CD8 antigen.
   h. Immunoglobins = antibodies; TCRs = antigen-receptors on T cells.
2. The major histocompatability complex (MHC) are self-antigens. T_H cells react with MHC II; T_C cells react with MHC I.
3. 

4. See Figure 17.20.
5. Activated T_C cells (CTLs) destroy target cells on contact. T_H cells interact with an antigen to "present" it to a B cell for antibody formation. T_R cells suppress the immune response. Cytokines are chemicals released by cells that initiate a response by other cells.
6. 

7. Both would prevent attachment of the pathogen; (a) interfere with the attachment site on the pathogen and (b) interfere with the pathogen's receptor site.
8. Rearrangement of the V region genes during embryonic development produces B cells with different antibody genes.
9. The person recovered because he or she produced antibodies against the pathogen. The memory response will continue to protect the person against that pathogen.
10. Dendritic cell

Multiple Choice

1. d	3. b	5. d	7. c	9. c
2. e	4. c	6. e	8. d	10. d

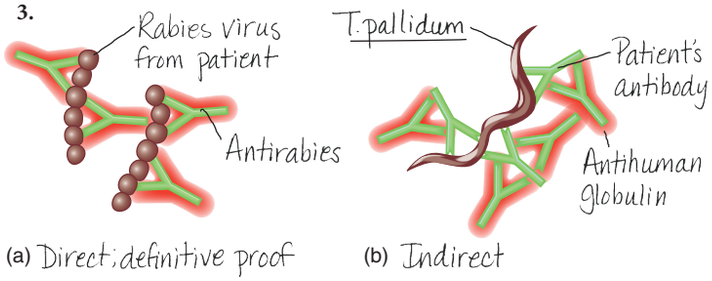
Chapter 18

Review

1. **a.** Whole-agent. Live, avirulent virus that can cause the disease if it mutates back to its virulent state.
   b. Whole-agent; (heat-) killed bacteria.
   c. Subunit; (heat- or formalin-) inactivated toxin.
   d. Subunit
   e. Subunit
   f. Conjugated
   g. Nucleic acid

2. **a.** Some viruses are able to agglutinate red blood cells. This reaction is used to detect the presence of large numbers of virions capable of causing hemagglutination (e.g., *Influenzavirus*).
   b. Antibodies produced against viruses that are capable of agglutinating red blood cells will inhibit the agglutination. Hemagglutination inhibition can be used to detect the presence of antibodies against these viruses.
   c. This is a procedure to detect antibodies that react with soluble antigens by first attaching the antigens to insoluble latex spheres. This procedure may be used to detect the presence of antibodies that develop during certain mycotic or helminthic infections.

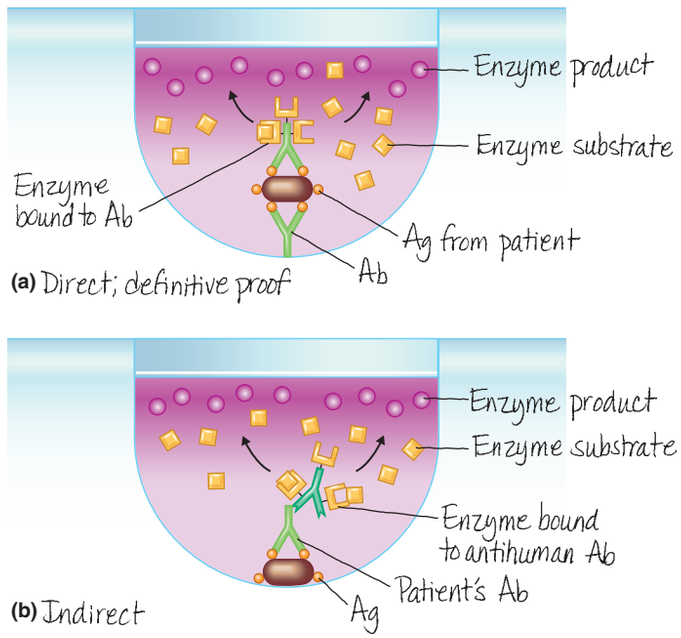
3.



4. See Figure 18.2.

5. If excess antibody is present, an antigen will combine with several antibody molecules. If excess antigen is present, an antibody will combine with several antigens. Refer to Figure 18.3.

6.



7. Particulate antigens react in agglutination reactions. The antigens can be cells or soluble antigens bound to synthetic particles. Soluble antigens take part in precipitation reactions.

8. **a.** 5 **d.** 3
   b. 4, 6 **e.** 6
   c. 1 **f.** 2, 4

9. **a.** 5 **d.** 6
   b. 3 **e.** 2
   c. 1 **f.** 4

10. Positive tuberculin skin test; the person has antibodies against *M. tuberculosis*.

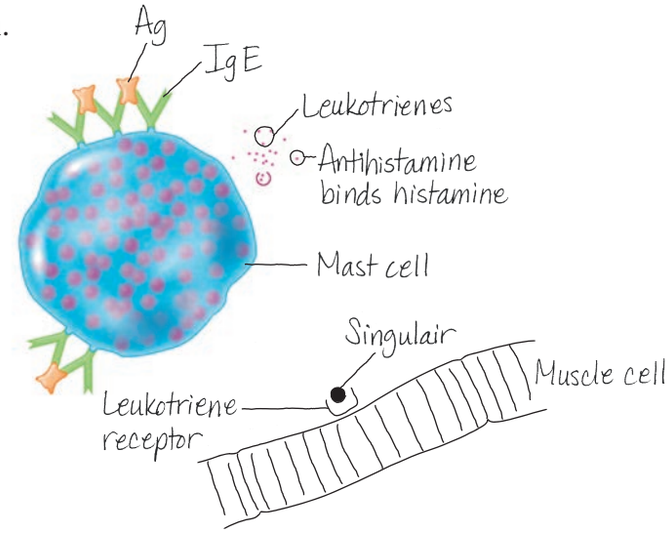
Multiple Choice

1. c	**3.** b	**5.** a	**7.** c	**9.** b
2. d	**4.** c	**6.** b	**8.** a	**10.** c

Chapter 19

Review

1.



2. Recipient's serum contains complement; activated complement causes hemolysis.

3. Recipient's antibodies will react with donor's tissues.

4. Refer to Figure 19.7.
   a. The observed symptoms are due to lymphokines.
   b. When a person contacts poison oak initially, the antigen (catechols on the leaves) binds to tissue cells, is phagocytized by macrophages, and is presented to receptors on the surface of T cells. Contact between the antigen and the appropriate T cell stimulates the T cell to proliferate and become sensitized. With subsequent exposure to the antigen, sensitized T cells release lymphokines, and a delayed hypersensitivity occurs.
   c. Small repeated doses of the antigen are believed to cause the production of IgG (blocking) antibodies.

5. Lupus patients have antibodies directed at their own DNA.

6. Cytotoxic: Antibodies react with cell-surface antigens.
   Immune complex: Antibody–complement complexes deposit in tissues.
   Cell-mediated: T cells destroy self cells. See Table 19.1.

7. Natural
   Inherited
   Viral infections, most notably HIV
   Artificial
   Induced by immunosupression drugs
   Result: Increased susceptibility to various infections depending on the type of immune deficiency.

8. Tumor cells have tumor-specific antigens such as TSTA and T antigen. Sensitized T_C cells may react with tumor-specific antigens, initiating lysis of the tumor cells.

9. Some malignant cells can escape the immune system by antigen modulation or immunological enhancement. Immunotherapy might trigger immunological enhancement. The body's defense against cancer is

cell-mediated and not humoral. Transfer of lymphocytes could cause graft-versus-host disease.

10. IgE antibody

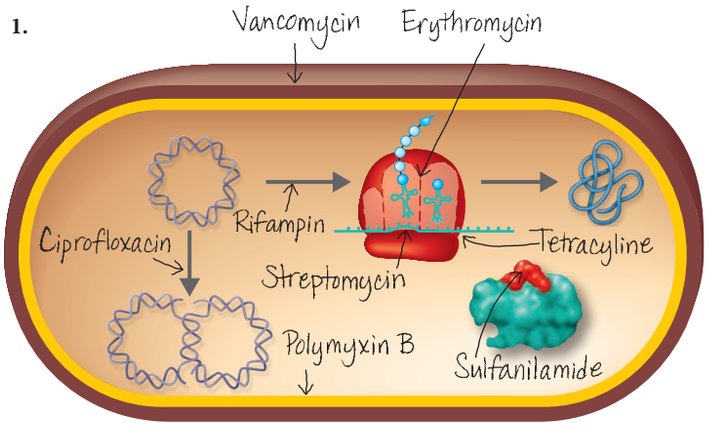
Multiple Choice

1. b	**3.** b	**5.** d	**7.** a	**9.** c
2. b	**4.** a	**6.** e	**8.** d	**10.** b

Chapter 20

Review

1.



2. The drug (1) should exhibit selective toxicity; (2) should have a broad spectrum; (3) should not produce hypersensitivity in the host; (4) should not produce drug resistance; and (5) should not harm normal microbiota.

3. Because a virus uses the host cell's metabolic machinery, it is difficult to damage the virus without damaging the host. Fungi, protozoa, and helminths possess eukaryotic cells. Therefore, antiviral, antifungal, antiprotozoan, and antihelminthic drugs must also affect eukaryotic cells.

4. Drug resistance is the lack of susceptibility of a microorganism to a chemotherapeutic agent. Drug resistance may develop when microorganisms are constantly exposed to an antimicrobial agent. Ways to minimize the development of drug-resistant microorganisms include judicious use of antimicrobial agents; following directions on the prescription; or administering two or more drugs simultaneously.

5. Simultaneous use of two agents can prevent the development of resistant strains of microorganisms, take advantage of the synergistic effect, provide therapy until a diagnosis is made, and lessen the toxicity of individual drugs by reducing the dosage of each in combination. One problem that can result from simultaneous use of two agents is an antagonistic effect.

6. **a.** Like polymyxin B, causes leaks in the plasma membrane.
b. Interferes with translation.

7. **a.** Inhibits formation of peptide bond.
b. Prevents translocation of ribosome along mRNA.
c. Interferes with attachment of tRNA to mRNA-ribosome complex.
d. Changes shape of 30S portion of ribosome, resulting in misreading mRNA.
e. Prevents 70S ribosomal subunits from forming.
f. Prevents release of peptide from ribosome.

8. DNA polymerase adds bases to the 3′–OH.

9. **a.** Penicillin inhibits bacterial cell wall synthesis. Echinocandin inhibits fungal cell wall synthesis.
b. Imidazole interferes with fungal plasma membrane synthesis. Polymyxin B disrupts any plasma membrane.

10. Human immunodeficiency virus

Multiple Choice

1. b	**3.** a	**5.** a	**7.** e	**9.** c
2. a	**4.** b	**6.** d	**8.** b	**10.** c

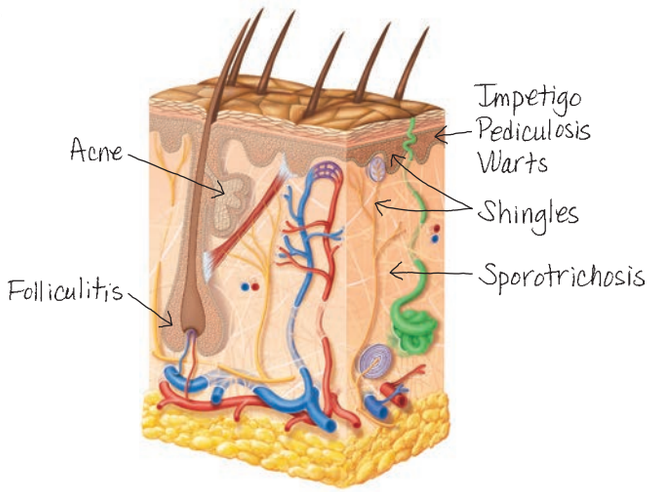
Chapter 21

Review

1. Bacteria usually enter through inapparent openings in the skin. Fungal pathogens (except subcutaneous) often grow on the skin itself. Viral infections of the skin (except warts and herpes simplex) most often gain access to the body through the respiratory tract.

2. *Staphylococcus aureus; Streptococcus pyogenes*

3.



4.

Etiological Agent	Clinical Symptoms	Mode of Transmission
P. acnes	Infected oil glands	Direct contact
S. aureus	Infected hair follicles	Direct contact
Papovavirus	Benign tumor	Direct contact
Herpesvirus	Vesicular rash	Respiratory route
Enteroviruses	Flat or raised rash	Direct contact
Paramyxovirus	Papular rash, Koplik's spots	Respiratory route
Togavirus	Macular rash	Respiratory route

5. The test determines the woman's susceptibility to rubella. If the test is negative, she is susceptible to the disease. If she acquires the disease during pregnancy, the fetus could become infected. A susceptible woman should be vaccinated.

6.

Symptoms	Disease
Koplik's spots	Measles
Macular rash	Measles
Vesicular rash	Chickenpox
Small, spotted rash	German measles
"Blisters"	Cold sore
Corneal ulcer	Keratoconjunctivitis

7. The central nervous system can be invaded following keratoconjunctivitis; this results in encephalitis.

8. Attenuated measles, mumps, and rubella viruses.

9. The patient has scabies, an infestation of mites in the skin. It is treated with permethrin insecticide or gamma benzene hexachloride. The presence of a six-legged arthropod (insect) indicates pediculosis (lice).

10. *Propionibacterium acnes*

Multiple Choice

1. c	**3.** b	**5.** d	**7.** e	**9.** a
2. d	**4.** c	**6.** d	**8.** d	**10.** d

Chapter 22

Review

1. The symptoms of tetanus are due to neurotoxin, not to bacterial growth (infection and inflammation).

2. **a.** Vaccination with tetanus toxoid.
b. Immunization with antitetanus toxin antibodies.

3. "Improperly cleaned" because *C. tetani* is found in soil that might contaminate a wound. "Deep puncture" because it is likely to be anaerobic. "No bleeding" because a flow of blood ensures an aerobic environment and some cleansing.

4. Etiology—Picornavirus (poliovirus).
Transmission—Ingestion of contaminated water.
Symptoms—Headache, sore throat, fever, nausea; rarely paralysis.
Prevention—Sewage treatment.
These vaccinations provide artificially acquired active immunity because they cause the production of antibodies, but they do not prevent or reverse damage to nerves.

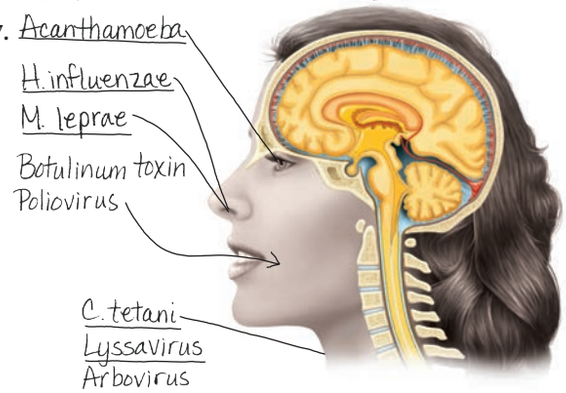
5.

Causative Agent	Susceptible Population	Transmission	Treatment
N. meningitidis	Children; military recruits	Respiratory	Penicillin
H. influenzae	Children	Respiratory	Rifampin
S. pneumoniae	Children; elderly	Respiratory	Penicillin
L. monocytogenes	Anyone	Foodborne	Penicillin
C. neoformans	Immunosuppressed individuals	Respiratory	Amphotericin B

6.

Disease	Etiology	Transmission	Symptoms	Treatment
Arboviral encephalitis	Togaviruses, Arboviruses	Mosquitoes (*Culex*)	Headache, fever, coma	Immune serum
African trypanosomiasis	*T. b. gambiense, T. b. rhodesiense*	Tsetse fly	Decreased physical activity and mental acuity	Suramm; melarsoprol
Botulism	*C. botulinum*	Ingestion	Flaccid paralysis	Antitoxin
Leprosy	*M. leprae*	Direct contact	Areas of sensation loss in skin	Dapsone

7.



8. Postexposure treatment—Passive immunization with antibodies followed by active immunization with HDCV. Preexposure treatment—Active immunization with HDCV.

Following exposure to rabies, antibodies are needed immediately to inactivate the virus. Passive immunization provides these antibodies. Active immunization will provide antibodies over a longer period of time, but they are not formed immediately.

9. The causative agent of Creutzfeldt-Jakob disease (CJD) is transmissible. Although there is some evidence for an inherited form of the disease, it has been transmitted by transplants. Similarities with viruses are (1) the prion cannot be cultured by conventional bacteriological techniques and (2) the prion is not readily seen in patients with CJD.

10. *Cryptococcus neoformans*

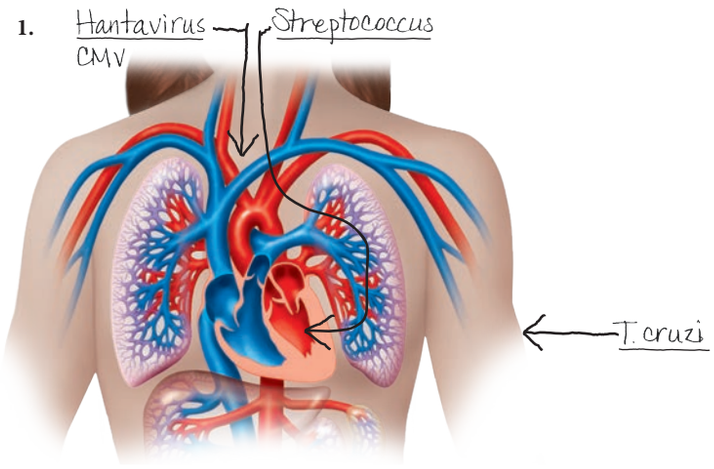
Multiple Choice

1. a	**3.** a	**5.** a	**7.** b	**9.** c
2. c	**4.** b	**6.** c	**8.** a	**10.** a

Chapter 23

Review

1.



2.

Disease	Causative Agent	Predisposing Conditions
p.s.	*Str. pyogenes*	Abortion or childbirth
s.b.e.	alpha-hemolytic strep.	Preexisting lesions
a.b.e.	*Sta. aureus*	Abnormal heart valves
r.f.	*Str. pyogenes*	Autoimmune

3. All are vectorborne rickettsial diseases. They differ from each other in (1) etiologic agent, (2) vector, (3) severity and mortality, and (4) incidence (e.g., epidemic, sporadic).

4.

Causative Agent	Vector	Treatment
Plasmodium	*Anopheles*	Quinine derivative
Flavivirus	*Aedes aegypti*	None
Flavivirus	*Aedes aegypti*	None
Borrelia	Soft ticks	Tetracycline
Leishmania	Sandflies	Antimony

5.

Disease	Causative Agent	Transmission	Reservoir
Tularemia	*Francisella tularensis*	Skin abrasions, ingestion, inhalation, bites	Rabbits
Brucellosis	*Brucella* spp.	Ingestion of milk, direct contact	Cattle
Anthrax	*Bacillus anthracis*	Skin abrasions, inhalation, ingestion	Soil, cattle
Lyme disease	*Borrelia burgdorferi*	Tick bites	Deer, mice
Ehrlichiosis	*Ehrlichia* spp.	Tick bites	Deer
Cytomegalic inclusion disease	HHV-5	Saliva, blood	Humans
Plague	*Yersinia pestis*	Flea bites, inhalation	Rodents

6.

Disease	Causative Agent	Transmission	Reservoir	Endemic Area
Schistosomiasis	*Schistosoma* spp.	Penetrate skin	Aquatic snail	Asia, South America
Toxoplasmosis	*Toxoplasma gondii*	Ingestion, inhalation	Cats	United States
Chagas' disease	*Trypanosoma cruzi*	"Kissing bug"	Rodents	Central America

7.

	Reservoir	Etiology	Transmission	Symptoms
Cat-scratch disease	Cats	*Bartonella henselae*	Scratch; touching eyes, fleas	Swollen lymph nodes, fever, malaise
Toxoplasmosis	Cats	*Toxoplasma gondii*	Ingestion	None, congenital infections, neurologic damage

8. Gangrenous tissue is anaerobic and has suitable nutrients for *C. perfringens*.

9. Infectious mononucleosis is caused by EB virus and is transmitted in oral secretions.

10. Rubella virus

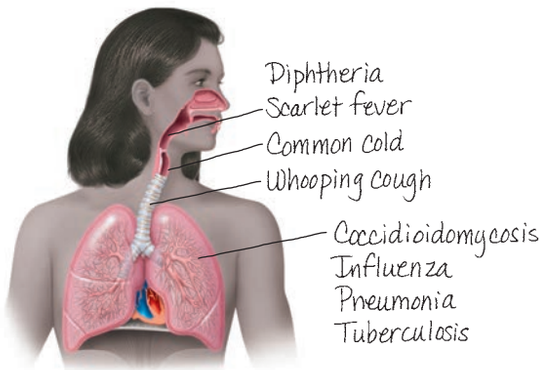
Multiple Choice

1. a **2.** e **3.** d **4.** c **5.** a **6.** c **7.** a **8.** c **9.** c **10.** c

Chapter 24

Review

1.



2. Mycoplasmal pneumonia is caused by *Mycoplasma pneumoniae* bacteria. Viral pneumonia can be caused by several different viruses. Mycoplasmal pneumonia can be treated with tetracyclines, whereas viral pneumonia cannot.

3.

Disease	Causative Agent	Symptoms
Upper Respiratory System		
Common cold	Coronaviruses	Sneezing, excessive nasal secretions, congestion
Lower Respiratory System		
Viral pneumonia	Several viruses	Fever, shortness of breath, chest pains
Influenza	Influenzavirus	Chills, fever, headache, muscular pains
RSV	Respiratory syncytial virus	Coughing, wheezing

Amantadine is used to treat influenza; palivizumab, for life-threatening RSV.

4.

Disease	Symptoms
Streptococcal pharyngitis	Pharyngitis and tonsillitis
Scarlet fever	Rash and fever
Diphtheria	Membrane across throat
Whooping cough	Paroxysmal coughing
Tuberculosis	Tubercles, coughing
Pneumococcal pneumonia	Reddish lungs, fever
H. influenzae pneumonia	Similar to pneumococcal pneumonia
Chamydial pneumonia	Low fever, cough, and headache
Otitis media	Earache
Legionellosis	Fever and cough
Psittacosis	Fever and headache
Q fever	Chills and chest pain
Epiglottitis	Inflamed, abscessed epiglottis
Melioidosis	Pneumonia

Refer to Diseases in Focus 24.1, 24.2, and 24.3 to complete the table.

5. Inhalation of large numbers of spores from *Aspergillus* or *Rhizopus* can cause infections in individuals with impaired immune systems, cancer, and diabetes.

6. No. Many different organisms (gram-positive bacteria, gram-negative bacteria, and viruses) can cause pneumonia. Each of these organisms is susceptible to different antimicrobial agents.

7.

Disease	Endemic Areas in the United States
Histoplasmosis	States adjoining the Mississippi and Ohio rivers
Coccidioidomycosis	American Southwest
Blastomycosis	Mississippi
Pneumocystis	Ubiquitous

Refer to Diseases in Focus 24.3 to complete the table.

8. In the tuberculin test, purified protein derivative (PPD) from *M. tuberculosis* is injected into the skin. Induration and reddening of the area around the injection site indicate an active infection or immunity to tuberculosis.

9. **a.** *Staphylococcus aureus*
   b. *Streptococcus pyogenes*
   c. *S. pneumoniae*
   d. *Corynebacterium diphtheriae*
   e. *Mycobacterium tuberculosis*
   f. *Moraxella catarrhalis*
   g. *Bordetella pertussis*
   h. *Burkholderia pseudomallei*
   i. *Legionella pneumophila*
   j. *Haemophilus influenzae*
   k. *Chlamydophila psittaci*
   l. *Coxiella burnetii*
   m. *Mycoplasma pneumoniae*

10. *Bordetella pertussis*

Multiple Choice

1. a	**3.** e	**5.** c	**7.** a	**9.** b
2. c	**4.** a	**6.** b	**8.** e	**10.** d

Chapter 25

Review

1.

	Causative Agent	Method of Transmission
Aflatoxin poisoning	*Aspergillus flavus*	Ingestion of toxin
Cryptosporidiosis	*Cryptosporidium hominis*	Ingestion
Pinworms	*Enterobius vermicularis*	Ingestion
Whipworms	*Trichuris trichiura*	Ingestion

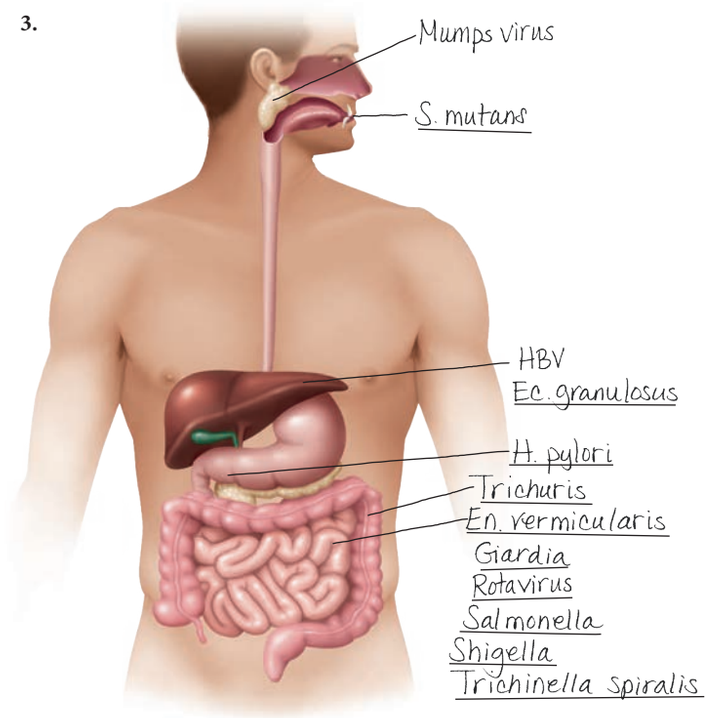
Refer to Diseases in Focus 25.5 to complete the table.

2.

Causative Agent	Suspect Foods	Prevention
V. parahaemolyticus	Oysters, shrimp	Cooking
V. cholerae	Water	
E. coli O157	Water, vegetables, ground beef	Cooking
C. jejuni	Chicken	Cooking
Y. enterocolitica	Meat, milk	Cooking
C. perfringens	Meat	Refrigeration after cooking
B. cereus	Rice dishes	Refrigeration after cooking
S. aureus	Creamy, salty	Refrigerating food
S. enterica	Eggs, poultry, vegetables	Cooking
Shigella spp.	Water, environmental fecal contamination	Disinfection

Refer to Diseases in Focus 25.2 to complete the table.

3.



4. Certain strains of *E. coli* may produce an enterotoxin or invade the epithelium of the large intestine.

5. Toxin produced by fungi; see p. 732.

6. All four are caused by protozoa. The infections are acquired by ingesting protozoa in contaminated water. Giardiasis is a prolonged diarrhea. Amebic dysentery is the most severe dysentery, with blood and mucus in the stools. *Cryptosporidium* and *Cyclospora* produce severe diseases in persons with immunodeficiencies.

7. **Food intoxication:** Microorganisms must be allowed to grow in food from the time of preparation to the time of ingestion. This usually occurs when foods are stored unrefrigerated or improperly canned. The etiologic agents (*Staphylococcus aureus* or *Clostridium botulinum*) must produce an exotoxin. Onset: 1 to 48 hours. Duration: A few days. Treatment: Antimicrobial agents are ineffective. The patient's symptoms may be treated.

   Food infection: Viable microorganisms must be ingested with food or water. The organisms could be present during preparation and survive cooking or be inoculated during later handling. The etiologic agents are usually gram-negative organisms (*Salmonella, Shigella, Vibrio,* and *Escherichia*) that produce endotoxins. *Clostridium perfringens* is a gram-positive bacterium that causes food infection. Onset: 12 hours to 2 weeks. Duration: Longer than intoxication because the microorganisms are growing in the patient. Treatment: Rehydration.

8.

Disease	Site	Symptoms
Mumps	Parotid glands	Inflammation of the parotid glands and fever
Hepatitis A	Liver	Anorexia, fever, diarrhea
Hepatitis B	Liver	Anorexia, fever, joint pains, jaundice
Viral gastroenteritis	Lower GI tract	Nausea, diarrhea, vomiting

Refer to Diseases in Focus 25.3 and 25.4 to complete this question.

9. Cook meat thoroughly. Eliminate the source of contamination to cattle and pigs.

10. *Giardia*

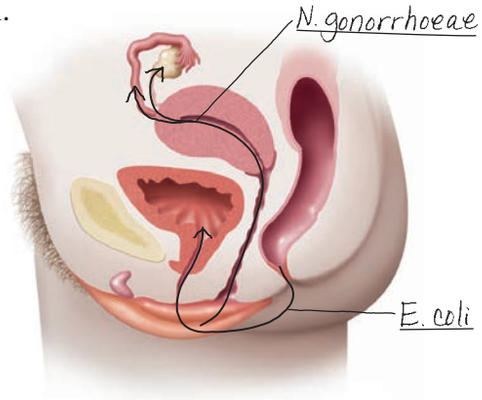
Multiple Choice

1. d	**3.** e	**5.** e	**7.** b	**9.** a
2. e	**4.** b	**6.** b	**8.** e	**10.** d

Chapter 26

Review

1.



2. Urinary tract infections may be transmitted by improper personal hygiene and contamination during medical procedures. They are often caused by opportunistic pathogens.

3. The proximity of the anus to the urethra and the relatively short length of the urethra can allow contamination of the urinary bladder in females. Gastrointestinal infections are also a predisposing factor for cystitis in females.

4. *Escherichia coli* causes about 75% of the cases. Portals of entry are from the lower urinary tract or systemic infections.

5.

Disease	Symptoms	Diagnosis
Bacterial vaginosis	Fishy odor	Odor, pH, clue cells
Gonorrhea	Painful urination	Isolation of *Neisseria*
Syphilis	Chancre	FTA–ABS
PID	Abdominal pain	Culture of pathogen
NGU	Urethritis	Absence of *Neisseria*
LGV	Lesion, lymph node enlargement	Observation of *Chlamydia* in cells
Chancroid	Swollen ulcer	Isolation of *Haemophilus*

Refer to Diseases in Focus 26.2 and 26.3 to complete table.

6. Symptoms—Burning sensation, vesicles, painful urination.
Etiology—Herpes simplex virus type 2 (sometimes type 1). When the lesions are not present, the virus is latent and noncommunicable.

7. *Candida albicans*—Severe itching; thick, yellow, cheesy discharge.
Trichomonas vaginalis—Profuse yellow discharge with disagreeable odor.

8.

Disease	Prevention of Congenital Disease
Gonorrhea	Treatment of newborn's eyes
Syphilis	Prevention and treatment of mother's disease
NGU	Treatment of newborn's eyes
Genital herpes	Cesarean delivery during active infection

9. *Chlamydia trachomatis*

Multiple Choice

1. b	**3.** a	**5.** d	**7.** c	**9.** b
2. e	**4.** c	**6.** c	**8.** b	**10.** a

Chapter 27

Review

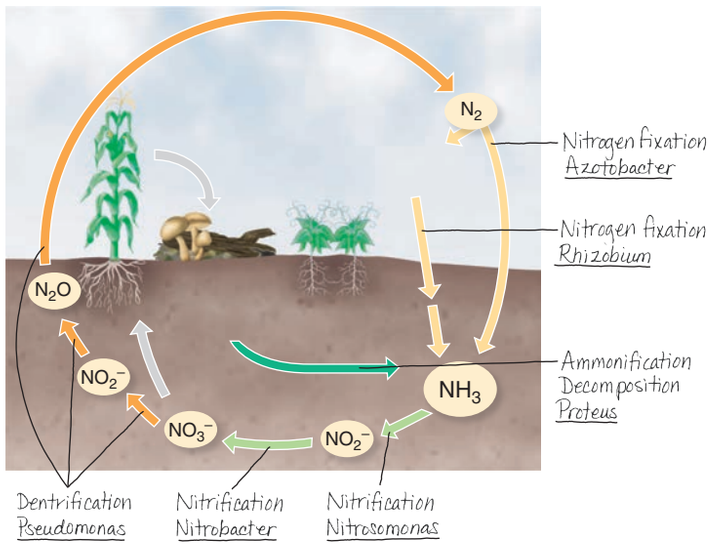
1. The koala should have an organ housing a large population of cellulose-degrading microorganisms.

2. *Penicillium* might make penicillin to reduce competition from faster-growing bacteria.

3. **a.** Amino acids
b. SO_4^{2-}
c. plants and bacteria
d. H_2S
e. carbohydrates
f. S^0

4. Phosphorus must be available for all organisms.

5.



6. Cyanobacteria: With fungi, cyanobacteria act as the photoautotrophic partner in a lichen; they may also fix nitrogen in the lichen. With *Azolla*: they fix nitrogen.
Mycorrhizae: Fungi that grow in and on the roots of higher plants; increase absorption of nutrients.
Rhizobium: In root nodules of legumes; fix nitrogen.
Frankia: In root nodules of alders, roses, and other plants; fix nitrogen.

7. Settling
Flocculation treatment
Sand filtration (or activated charcoal filtration)
Chlorination
The amount of treatment prior to chlorination depends on the amount of inorganic and organic matter in the water.

8. **a.** 2 **e.** 3
b. 1 **f.** 2
c. 2 **g.** 3
d. 2

9. Biodegradation of sewage, herbicides, oil, or PCBs.

10. Cyanobacteria (*Anabaena*)

Multiple Choice

1. a	**3.** b	**5.** c	**7.** b	**9.** e
2. b	**4.** b	**6.** c	**8.** b	**10.** c

Chapter 28

Review

1. Industrial microbiology is the science of using microorganisms to produce products or accomplish a process. Industrial microbiology provides (1) chemicals such as antibiotics that would not otherwise be available, (2) processes to remove or detoxify pollutants, (3) fermented foods that have desirable flavors or enhanced shelf life, and (4) enzymes for manufacturing a variety of goods.

2. The goal of commercial sterilization is to eliminate spoilage and disease-causing organisms. The goal of hospital sterilization is complete sterilization.

3. The acid in the berries will prevent the growth of some microbes.

4. Milk $\xrightarrow{\text{Lactic Acid Bacteria}}$ Curd + Whey

↓ ↓

Cheese Waste

Hard cheese is ripened by lactic acid bacteria growing anaerobically in the interior of the curd. Soft cheese is ripened by molds growing aerobically on the outside of the curd.

5. Nutrients must be dissolved in water; water is also needed for hydrolysis. Malt is the carbon and energy source that the yeast will ferment to make alcohol. Malt contains glucose and maltose from the action of amylases on starch in seeds (e.g., barley).

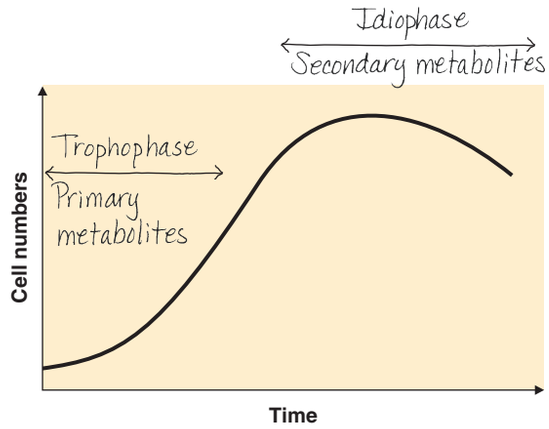
6. A bioreactor provides the following advantages over simple flask containers:

- Larger culture volumes can be grown.
- Process instrumentation for monitoring and controlling critical environmental conditions such as pH, temperature, dissolved oxygen, and aeration can be used.
- Sterilization and cleaning systems are designed in place.
- It offers aseptic sampling and harvest systems for in-process sampling.
- Improved aeration and mixing characteristics result in improved cell growth and high final cell densities.
- A high degree of automation is possible.
- Process reproducibility is improved.

7. (1) Enzymes don't produce hazardous wastes. (2) Enzymes work under reasonable conditions, e.g., they don't require high temperatures or acidity. (3) Use of enzymes eliminates the need to use petroleum in chemical syntheses of solvents such as alcohol and acetone. (4) Enzymes are biodegradable. (5) Enzymes are not toxic.

8. The production of ethyl alcohol from corn; or methane from sewage. Alcohols and hydrogen are produced by fermentation; methane is produced by anaerobic respiration.

9.



10. *Saccharomyces cerevisiae*

Multiple Choice

1. c	**3.** e	**5.** b	**7.** e	**9.** b
2. b	**4.** c	**6.** c	**8.** a	**10.** a

Appendix A

Metabolic Pathways

Please scan this QR code or visit the MasteringMicrobiology Study Area to see the metabolic pathways, including the Calvin-Benson cycle for photosynthetic carbon metabolism, glycolysis, the pentose phosphate pathway, the Entner-Doudoroff pathway, and the Krebs cycle.



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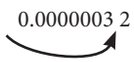
Appendix B

Exponents, Exponential Notation, Logarithms, and Generation Time

Exponents and Exponential Notation

Very large and very small numbers, such as 4,650,000,000 and 0.00000032, are cumbersome to work with. It is more convenient to express such numbers in exponential notation—that is, as a power of 10. For example, 4.65×10^9 is in standard exponential notation, or **scientific notation:** 4.65 is the *coefficient,* and 9 is the power or *exponent.* In standard exponential notation, the coefficient is always a number between 1 and 10, and the exponent can be positive or negative.

To change a number into exponential notation, follow two steps. First, determine the coefficient by moving the decimal point so there is only one nonzero digit to the left of it. For example,



The coefficient is 3.2. Second, determine the exponent by counting the number of places you moved the decimal point. If you moved it to the left, the exponent is positive. If you moved it to the right, the exponent is negative. In the example, you moved the decimal point seven places to the right, so the exponent is –7. Thus

$$0.00000032 = 3.2 \times 10^{-7}$$

Now suppose you are working with a larger number instead of a very small number. The same rules apply, but the exponential value will be positive rather than negative. For example,

$$4{,}650{,}000{,}000 = 4.65 \times 10^9$$

To multiply numbers written in exponential notation, multiply the coefficients and *add* the exponents. For example,

$$(3 \times 10^4) \times (2 \times 10^3) =$$
$$(3 \times 2) \times (10^{4+3}) = 6 \times 10^7$$

To divide, divide the coefficient and *subtract* the exponents. For example,

$$\frac{3 \times 10^4}{2 \times 10^3} = \frac{3}{2} \times 10^{4-3} = 1.5 \times 10^1$$

Microbiologists use exponential notation in many situations. For instance, exponential notation is used to describe the number of microorganisms in a population. Such numbers are often very large (see Chapter 6). Another application of exponential notation is to express concentrations of chemicals in a solution—chemicals such as media components (Chapter 6), disinfectants (Chapter 7), or antibiotics (Chapter 20). Such numbers are often very small. Converting from one unit of measurement to another in the metric system requires multiplying or dividing by a power of 10, which is easiest to carry out in exponential notation.

Logarithms

A **logarithm (log)** is the power to which a base number is raised to produce a given number. Usually we work with logarithms to the base 10, abbreviated $\log_{10}$. The first step in finding the $\log_{10}$ of a number is to write the number in standard exponential notation. If the coefficient is exactly 1, the $\log_{10}$ is simply equal to the exponent. For example

$$\log_{10} 0.00001 = \log_{10} (1 \times 10^{-5})$$
$$= -5$$

If the coefficient is not 1, as is often the case, the logarithm function on a calculator must be used to determine the logarithm.

Microbiologists use logs for calculating pH levels and for graphing the growth of microbial populations in culture (see Chapter 6).

Calculating Generation Time

As a cell divides, the population increases exponentially. Numerically this is equal to 2 (because one cell divides into two) raised to the number of times the cell divided (generations);

$$2^{\text{number of generations}}$$

To calculate the final concentration of cells:

$$\text{Initial number of cells} \times 2^{\text{number of generations}} = \text{Number of cells}$$

For example, if 5 cells were allowed to divide 9 times, this would result in

$$5 \times 2^9 = 2560 \text{ cells}$$

To calculate the number of generations a culture has undergone, cell numbers must be converted to logarithms. Standard logarithm values are based on 10. The log of 2 (0.301) is used because one cell divides into two.

$$\text{Number of generations} = \frac{\text{log number of cells (end)} - \text{log number of cells (beginning)}}{0.301}$$

To calculate the generation of time for a population:

$$\frac{60 \text{ min/hr} \times \text{hours}}{\text{number of generations}} = \textit{minutes/generation}$$

As an example, we will calculate the generation time if 100 bacterial cells growing for 5 hours produced 1,720,320 cells:

$$\frac{\log 1{,}720{,}320 - \log 100}{0.301} = 14 \text{ generations}$$

$$\frac{60 \text{ min/hr} \times 5 \text{ hours}}{14 \text{ generations}} = 21 \text{ minutes/generation}$$

A practical application of the calculation is determining the effect of a newly developed food preservative on the culture. Suppose 900 of the same species were grown under the same conditions as the previous example, except that the preservative was added to the culture medium. After 15 hours, there were 3,276,800 cells. Calculate the generation time, and decide whether the preservative inhibited growth.

Answer: 75 minutes/generation. The preservative did inhibit growth.

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Appendix C

Methods for Taking Clinical Samples

To diagnose a disease, it is often necessary to obtain a sample of material that may contain the pathogenic microorganism. Samples must be taken aseptically. The sample container should be labeled with the patient's name, room number (if hospitalized), date, time, and medications being taken. Samples must be transported to the laboratory immediately for culture. Delay in transport may result in the growth of some organisms, and their toxic products may kill other organisms. Pathogens tend to be fastidious and die if not kept in optimum environmental conditions.

In the laboratory, samples from infected tissues are cultured on differential and selective media in an attempt to isolate and identify any pathogens or organisms that are not normally found in association with that tissue.

Universal Precautions*

The following procedures should be used by all health care workers, including students, whose activities involve contact with patients or with blood or other body fluids. These procedures were developed to minimize the risk of transmitting HIV or AIDS in a health care environment, but adherence to these guidelines will minimize the transmission of *all* nosocomial infections.

1. Gloves should be worn when touching blood and body fluids, mucous membranes, and nonintact skin and when handling items or surfaces soiled with blood or body fluids. Gloves should be changed after contact with each patient.
2. Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids. Hands should be washed immediately after gloves are removed.
3. Masks and protective eyewear or face shields should be worn during procedures that are likely to generate droplets of blood or other body fluids.
4. Gowns or aprons should be worn during procedures that are likely to generate splashes of blood or other body fluids.
5. To prevent needlestick injuries, needles should not be recapped, purposely bent or broken, or otherwise manipulated by hand. After disposable syringes and needles, scalpel blades, and other sharp items are used, they should be placed in puncture-resistant containers for disposal.
6. Although saliva has not been implicated in HIV transmission, mouthpieces, resuscitation bags, and other ventilation devices should be available for use in areas in which the need for resuscitation is predictable. Emergency mouth-to-mouth resuscitation should be minimized.
7. Health care workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient-care equipment.
8. Pregnant health care workers are not known to have a greater risk of contracting HIV infection than health care workers who are not pregnant; however, if a health care worker develops HIV infection during pregnancy, the infant is at risk of infection. Because of this risk, pregnant health care workers should be especially familiar with, and strictly adhere to, precautions to minimize the risk of HIV transmission.

Instructions for Specific Sampling Procedures

Wound or Abscess Culture

1. Cleanse the area with a sterile swab moistened in sterile saline.
2. Disinfect the area with 70% ethanol or iodine solution.
3. If the abscess has not ruptured spontaneously, a physician will open it with a sterile scalpel.
4. Wipe the first pus away.
5. Touch a sterile swab to the pus, taking care not to contaminate the surrounding tissue.
6. Replace the swab in its container, and properly label the container.

Ear Culture

1. Clean the skin and auditory canal with 1% tincture of iodine.
2. Touch the infected area with a sterile cotton swab.
3. Replace the swab in its container.

Eye Culture

This procedure is often performed by an ophthalmologist.

1. Anesthetize the eye with topical application of a sterile anesthetic solution.
2. Wash the eye with sterile saline solution.
3. Collect material from the infected area with a sterile cotton swab. Return the swab to its container.

Blood Culture

1. Close the room's windows to avoid contamination.
2. Clean the skin around the selected vein with 2% tincture of iodine on a cotton swab.
3. Remove dried iodine with gauze moistened with 80% isopropyl alcohol.
4. Draw a few milliliters of venous blood.
5. Aseptically bandage the puncture.

Urine Culture

1. Provide the patient with a sterile container.
2. Instruct the patient to first void a small volume from the urinary bladder before collection (to wash away extraneous bacteria of the skin microbiota) then to collect a midstream sample.
3. A urine sample may be stored under refrigeration (4–6°C) for up to 24 hours.

Fecal Culture

For bacteriological examination, only a small sample is needed. This may be obtained by inserting a sterile swab into the rectum or feces. The swab is then placed in a tube of sterile enrichment broth for transport to the laboratory. For examination for parasites, a small sample may be taken from a morning stool. The sample is placed in a preservative (polyvinyl alcohol, buffered glycerol, saline, or formalin) for microscopic examination for eggs and adult parasites.

Sputum Culture

1. A morning sample is best because microorganisms will have accumulated while the patient is sleeping.
2. The patient should rinse his or her mouth thoroughly to remove food and normal microbiota.
3. The patient should cough deeply from the lungs and expectorate into a sterile glass wide-mouth jar.
4. Care should be taken to avoid contaminating health care workers.
5. In cases such as tuberculosis in which there is little sputum, stomach aspiration may be necessary.
6. Infants and children tend to swallow sputum. A fecal sample may be of some value in these cases.

Source: Centers for Disease Control and Prevention and National Institutes of Health. *Biosafety in Microbiological and Biomedical Laboratories.*

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Appendix D

Pronunciation of Scientific Names

Rules of Pronunciation

The easiest way to learn new material is to talk about it, and that requires saying scientific names. Scientific names may look difficult at first glance, but keep in mind that generally every *syllable* is pronounced. The primary requirement in saying a scientific name is to communicate it.

The rules for the pronunciation of scientific names depend, in part, on the derivation of the root word and its vowel sounds. We have provided some general guidelines here. Pronunciations frequently do not follow the rules because a common usage has become "accepted" or the derivation of the name cannot be determined. For many scientific names there are alternative correct pronunciations.

Vowels

Pronounce all the vowels in scientific names. Vowels marked with a line above the letter are pronounced with a long sound, as in *rate (rāt)*. Vowels not marked by a line above the letter are pronounced as a short sound, as in *rat*. Two vowels written together and pronounced as one sound are called a *diphthong* (for example, the *ou* in *sound*). A special comment is needed about the pronunciation of the vowel endings *-i* and *-ae:* There are two alternative ways to pronounce each of these. In this book, we usually give the pronunciation of a long *e (ē)* to the *-i* ending, and a long *i (ī)* to the *-ae* ending. However, the reverse pronunciations are also correct and in some cases are preferred. For example, *coli* is usually pronounced KŌ-lī. Other vowel sounds are *oy* as in *oil* and *oo* as in *boot*.

Consonants

When *c* or *g* is followed by *ae, e, oe, i,* or *y,* it has a soft sound. Examples of words with soft *c* and *g* include *circus* and *giraffe*. When *c* or *g* is followed by *a, o, oi,* or *u,* it has a hard sound. When a double *c* is followed by *e, i,* or *y,* it is pronounced as *ks* (e.g., *cocci*).

Accent

The accented syllable is usually the next-to-last or third-to-last syllable. The most strongly accented syllable appears in capital letters. A secondary accent is noted with a prime (′), as in *Staphylococcus* (STAF-i-lō-kok′kus).

1. The accent is on the next-to-last syllable:
   a. When the name contains only two syllables. Example: PES-tis.
   b. When the next-to-last syllable is a diphthong. Example: ah-kan-thah-MĒ-bah.
   c. When the vowel of the next-to-last syllable is long. Example: trep-ō-NĒ-mah. The vowel in the next-to-last syllable is long in words ending in the following suffixes:

Suffix	Example
-ales	Orders such as Eubacteriales
-ina	*Sarcina*
-anus,-anum	*pasteurianum*
-uta	*diminuta*

   d. When the word ends in one of the following suffixes:

Suffix	Example
-atus,-atum	*caudatum*
-ella	*Salmonella*

2. The accent is on the third-to-last syllable in family names. Families end in *-aceae,* which is always pronounced -Ā-sē-ē. The most strongly accented syllable appears in capital letters. A secondary accent is noted with a prime (′). For example *Staphylococcus* (STAF-i-lō-kok′kus).

Pronunciation of Microorganisms in this Text

Pronunciation key:

a	hat	g	go	ō	go	u	cup
ā	age	i	sit	or	order	ū	use
ah	father	ī	ice	oo	boot	x	zero
ch	child	ks	tax	oy	oil	z	zero
e	let	kw	quiz	ou	out	zh	seizure
ē	see	ng	long	sh	she		
er	term	o	hot	th	thin		

Please scan this QR code or visit the MasteringMicrobiology Study Area to see a list of pronunciations of microorganisms in this text.

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Appendix E

Word Roots Used in Microbiology

The Latin rules of grammar pertain to singular and plural forms of scientific names.

	Gender		
	Feminine	Masculine	Neuter
Singular	-a	-us	-um
Plural	-ae	-i	-a
Examples	alga, algae	fungus, fungi	bacterium, bacteria

a-, an- absence, lack. Examples: abiotic, in the absence of life; anaerobic, in the absence of air.
-able able to, capable of. Example: viable, having the ability to live or exist.
actino- ray. Example: actinomycetes, bacteria that form star-shaped (with rays) colonies.
aer- air. Examples: aerobic, in the presence of air; aerate, to add air.
albo- white. Example: *Streptomyces albus* produces white colonies.
ameb- change. Example: ameboid, movement involving changing shapes.
amphi- around. Example: amphitrichous, tufts of flagella at both ends of a cell.
amyl- starch. Example: amylase, an enzyme that degrades starch.
ana- up. Example: anabolism, building up.
ant-, anti- opposed to, preventing. Example: antimicrobial, a substance that prevents microbial growth.
archae- ancient. Example: archaeobacteria, "ancient" bacteria, thought to be like the first form of life.
asco- bag. Example: ascus, a baglike structure holding spores.
aur- gold. Example: *Staphylococcus aureus,* gold-pigmented colonies.
aut-, auto- self. Example: autotroph, self-feeder.
bacillo- a little stick. Example: bacillus, rod-shaped.
basid- base, pedestal. Example: basidium, a cell that bears spores.
bdell- leech. Example: *Bdellovibrio,* a predatory bacterium.
bio- life. Example: biology, the study of life and living organisms.
blast- bud. Example: blastospore, spores formed by budding.
bovi- cattle. Example: *Mycobacterium bovis,* a bacterium found in cattle.
brevi- short. Example: *Lactobacillus brevis,* a bacterium with short cells.
butyr- butter. Example: butyric acid, formed in butter, responsible for rancid odor.
campylo- curved. Example: *Campylobacter,* curved rod.
carcin- cancer. Example: carcinogen, a cancer-causing agent.
caseo- cheese. Example: caseous, cheeselike.
caul- a stalk. Example: *Caulobacter,* appendaged or stalked bacteria.
cerato- horn. Example: keratin, the horny substance making up skin and nails.
chlamydo- covering. Example: chlamydoconidia, conidia formed inside hypha.
chloro- green. Example: chlorophyll, green-pigmented molecule.
chrom- color. Examples: chromosome, readily stained structure; metachromatic, intracellular colored granules.
chryso- golden. Example: *Streptomyces chryseus,* golden colonies.
-cide killing. Example: bactericide, an agent that kills bacteria.
cili- eyelash. Example: cilia, a hairlike organelle.
cleisto- closed. Example: cleistothecium, completely closed ascus.
co-, con- together. Example: concentric, having a common center, together in the center.
cocci- a berry. Example: coccus, a spherical cell.
coeno- shared. Example: coenocyte, a cell with many nuclei not separated by septa.
col-, colo- colon. Examples: colon, large intestine; *Escherichia coli,* a bacterium found in the large intestine.
conidio- dust. Example, conidia, spores developed at the end of aerial hypha, never enclosed.
coryne- club. Example: *Corynebacterium,* club-shaped cells.
-cul small form. Example: particle, a small part.
-cut the skin. Example: Firmicutes, bacteria with a firm cell wall, gram-positive.
cyano- blue. Example: cyanobacteria, blue-green pigmented organisms.
cyst- bladder. Example: cystitis, inflammation of the urinary bladder.
cyt- cell. Example: cytology, the study of cells.
de- undoing, reversal, loss, removal. Example: deactivation, becoming inactive.
di-, diplo- twice, double. Example: diphlococci, pairs of cocci.
dia- through, between. Example: diaphragm, the wall through or between two areas.
dys- difficult, faulty, painful. Example: dysfunction, disturbed function.
ec-, ex-, ecto out, outside, away from. Example: excrete, to remove materials from the body.
en-, em- in, inside. Example: encysted, enclosed in a cyst.
entero- intestine. Example: *Enterobacter,* a bacterium found in the intestine.
eo- dawn, early. Example: *Eobacterium,* a 3.4-billion-year-old fossilized bacterium.
epi- upon, over. Example: epidemic, number of cases of a disease over the normally expected number.
erythro- red. Example: erythema, redness of the skin.
eu- well, proper. Example: eukaryote, a proper cell.
exo- outside, outer layer. Example: exogenous, from outside the body.
extra- outside, beyond. Example: extracellular, outside the cells of an organism.
firmi- strong. Example: *Bacillus firmus* forms resistant endospores.
flagell- a whip. Example: flagellum, a projection from a cell; in eukaryotic cells, it pulls cells in a whiplike fashion.
flav- yellow. Example: *Flavobacterium* cells produce yellow pigment.
fruct- fruit. Example: fructose, fruit sugar.
-fy to make. Example: magnify, to make larger.
galacto- milk. Example: galactose, monosaccharide from milk sugar.
gamet- to marry. Example: gamete, a reproductive cell.
gastr- stomach. Example: gastritis, inflammation of the stomach.
gel- to stiffen. Example: gel, a solidified colloid.
-gen an agent that initiates. Example: pathogen, any agent that produces disease.
-genesis formation. Example: pathogenesis, production of disease.
germ, germin- bud. Example: germ, part of an organism capable of developing.
-gony reproduction. Example: schizogony, multiple fission producing many new cells.
gracili- thin. Example: *Aquaspirillum gracile,* a thin cell.
halo- salt. Example: halophile, an organism that can live in high salt concentrations.
haplo- one, single. Example: haploid, half the number of chromosomes or one set.
hema-, hemato-, hemo- blood. Example: *Haemophilus,* a bacterium that requires nutrients from red blood cells.
hepat- liver. Example: hepatitis, inflammation of the liver.
herpes creeping. Example: herpes, or shingles, lesions appear to creep along the skin.
hetero- different, other. Example: heterotroph, obtains organic nutrients from other organisms; other feeder.
hist- tissue. Example: histology, the study of tissues.
hom-, homo- same. Example: homofermenter, an organism that produces only lactic acid from fermentation of a carbohydrate.

hydr-, hydro- water. Example: dehydration, loss of body water.
hyper- excess. Example: hypertonic, having a greater osmotic pressure in comparison with another.
hypo- below, deficient. Example: hypotonic, having a lesser osmotic pressure in comparison with another.
im- not, in. Example: impermeable, not permitting passage.
inter- between. Example: intercellular, between the cells.
intra- within, inside. Example: intracellular, inside the cell.
io- violet. Example: iodine, a chemical element that produces a violet vapor.
iso- equal, same. Example: isotonic, having the same osmotic pressure when compared with another.
-itis inflammation of. Example: colitis, inflammation of the large intestine.
-karyo, -caryo a nut. Example: eukaryote, a cell with a membrane-enclosed nucleus.
kin- movement. Example: streptokinase, an enzyme that lyses or moves fibrin.
lacti- milk. Example: lactose, the sugar in milk.
lepis- scaly. Example: leprosy, disease characterized by skin lesions.
lepto- thin. Example: *Leptospira,* thin spirochete.
leuko- whiteness. Example: leukocyte, a white blood cell.
lip-, lipo- fat, lipid. Example: lipase, an enzyme that breaks down fats.
-logy the study of. Example: pathology, the study of changes in structure and function brought on by disease.
lopho- tuft. Example: lophotrichous, having a group of flagella on one side of a cell.
luc-, luci- light. Example: luciferin, a substance in certain organisms that emits light when acted upon by the enzyme luciferase.
lute-, luteo- yellow. Example: *Micrococcus luteus,* yellow colonies.
-lysis loosening, to break down. Example: hydrolysis, chemical decomposition of a compound into other compounds as a result of taking up water.
macro- largeness. Example: macromolecules, large molecules.
mendosi- faculty. Example: mendosicutes, archaeobacteria lacking peptidoglycan.
meningo- membrane. Example: meningitis, inflammation of the membranes of the brain.
meso- middle. Example: mesophile, an organism whose optimum temperature is in the middle range.
meta- beyond, between, transition. Example: metabolism, chemical changes occurring within a living organism.
micro- smallness. Example: microscope, an instrument used to make small objects appear larger.
-mnesia memory. Examples: amnesia, loss of memory; anamnesia, return of memory.
molli- soft. Example: Mollicutes, a class of wall-less eubacteria.
-monas a unit. Example: *Methylomonas,* a unit (bacterium) that utilizes methane as its carbon source.
mono- singleness. Example: monotrichous, having one flagellum.
morpho- form. Example: morphology, the study of the form and structure of organisms.
multi- many. Example: multinuclear, having several nuclei.
mur- wall. Example: murein, a component of bacterial cell walls.
mus-, muri- mouse. Example: murine typhus, a form of typhus endemic in mice.
mut- to change. Example: mutation, a sudden change in characteristics.
myco-, -mycetoma, -myces a fungus. Example: *Saccharomyces,* sugar fungus, a genus of yeast.
myxo- slime, mucus. Example: Myxobacteriales, an order of slime-producing bacteria.
necro- a corpse. Example: necrosis, cell death or death of a portion of tissue.
-nema a thread. Example: *Treponema* has long, threadlike cells.
nigr- black. Example: *Aspergillus niger,* a fungus that produces black conidia.
ob- before, against. Example: obstruction, impeding or blocking up.
oculo- eye. Example: monocular, pertaining to one eye.
-oecium, -ecium a house. Examples: perithecium, an ascus with an opening that encloses spores; ecology, the study of the relationships among organisms and between an organism and its environment (household).
-oid like, resembling. Example: coccoid, resembling a coccus.
oligo- small, few. Example: oligiosaccharide, a carbohydrate composed of a few (7–10) monosaccharides.
-oma tumor. Example: lymphoma, a tumor of the lymphatic tissues.
-ont being, existing. Example: schizont, a cell existing as a result of schizogony.
ortho- straight, direct. Example: orthomyxovirus, a virus with a straight, tubular capsid.
-osis, -sis condition of. Examples: lysis, the condition of loosening; symbiosis, the condition of living together.
pan- all, universal. Example: pandemic, an epidemic affecting a large region.
para- beside, near. Example: parasite, an organism that "feeds beside" another.
peri- around. Example: peritrichous, projections from all sides.
phaeo- brown. Example: Phaeophyta, brown algae.
phago- eat. Example: phagocyte, a cell that engulfs and digests particles or cells.
philo-, -phil liking, preferring. Example: thermophile, an organism that prefers high temperatures.
-phore bears, carries. Example: conidiophore, a hypha that bears conidia.
-phyll leaf. Example: chlorophyll, the green pigment in leaves.
-phyte plant. Example: saprophyte, a plant that obtains nutrients from decomposing organic matter.
pil- a hair. Example: pilus, a hairlike projection from a cell.
plankto- wandering, roaming. Example: plankton, organisms drifting or wandering in water.
plast- formed. Example: plastid, a formed body within a cell.
-pnoea, -pnea breathing. Example: dyspnea, difficulty in breathing.
pod- foot. Example: pseudopod, a footlike structure.
poly- many. Example: polymorphism, many forms.
post- after, behind. Example: posterior, a place behind a (specific) part.
pre-, pro- before, ahead of. Examples: prokaryote, a cell with the first nucleus; pregnant, before birth.
pseudo- false. Example: pseudopod, false foot.
psychro- cold. Example: psychrophile, an organism that grows best at low temperatures.
-ptera wing. Example: Diptera, the order of true flies, insects with two wings.
pyo- pus. Example: pyogenic, pus-forming.
rhabdo- stick, rod. Example: rhabdovirus, an elongated, bullet-shaped virus.
rhin- nose. Example: rhinitis, inflammation of mucous membranes in the nose.
rhizo- root. Examples: *Rhizobium,* a bacterium that grows in plant roots; mycorrhiza, a fungus that grows in or on plant roots.
rhodo- red. Example: *Rhodospirillum,* a red-pigmented, spiral-shaped bacterium.
rod- gnaws. Example: rodents, the class of mammals with gnawing teeth.
rubri- red. Example: *Clostridiium rubrum,* red-pigmented colonies.
rumin- throat. Example: *Ruminococcus,* a bacterium associated with a rumen (modified esophagus).
saccharo- sugar. Example: disaccharide, a sugar consisting of two simple sugars.
sapr- rotten. Example: *Saprolegnia,* a fungus that lives on dead animals.
sarco- flesh. Example: sarcoma, a tumor of muscle or connective tissues.
schizo- split. Example: schizomycetes, organisms that reproduce by splitting and an early name for bacteria.
scolec- worm. Example: scolex, the head of a tapeworm.
-scope, -scopic watcher. Example: microscope, an instrument used to watch small things.
semi- half. Example: semicircular, having the form of half a circle.
sept- rotting. Example: septic, presence of bacteria that could cause decomposition.
septo- partition. Example: septum, a cross-wall in a fungal hypha.
serr- notched. Example: serrate, with a notched edge.
sidero- iron. Example: *Siderococcus,* a bacterium capable of oxidizing iron.
siphon- tube. Example: Siphonaptera, the order of fleas, insects with tubular mouths.
soma- body. Example: somatic cells, cells of the body other than gametes.

speci- particular things. Examples: species, the smallest group of organisms with similar properties; specify, to indicate exactly.
spiro- coil. Example: spirochete, a bacterium with a coiled cell.
sporo- spore. Example: sporangium, a structure that holds spores.
staphylo- grapelike cluster. Example: *Staphylococcus,* a bacterium that forms clusters of cells.
-stasis arrest, fixation. Example: bacteriostasis, cessation of bacterial growth.
strepto- twisted. Example: *Streptococcus,* a bacterium that forms twisted chains of cells.
sub- beneath, under. Example: subcutaneous, just under the skin.
super- above, upon. Example: superior, the quality or state of being above others.
sym-, syn- together, with. Examples: synapse, the region of communication between two neurons; synthesis, putting together.
-taxi to touch. Example: chemotaxis, response to the presence (touch) of chemicals.
taxis- orderly arrangement. Example: taxonomy, the science dealing with arranging organisms into groups.
tener- tender. Example: Tenericutes, the phylum containing wall-less eubacteria.
thallo- plant body. Example: thallus, an entire macroscopic fungus.
therm- heat. Example: *Thermus,* a bacterium that grows in hot springs (to 75°C).
thio- sulfur. Example: *Thiobacillus,* a bacterium capable of oxidizing sulfur-containing compounds.
-thrix See trich-.
-tome, -tomy to cut. Example: appendectomy, surgical removal of the appendix.
-tone, -tonic strength. Example: hypotonic, having less strength (osmotic pressure).
tox- poison. Example: antitoxin, effective against poison.
trans- across, through. Example: transport, movement of substances.
tri- three. Example: trimester, three-month period.
trich- a hair. Example: peritrichous, hairlike projections from cells.
-trope turning. Example: geotropic, turning toward the Earth (pull of gravity).
-troph food, nourishment. Example: trophic, pertaining to nutrition.
-ty condition of, state. Example: immunity, the condition of being resistant to disease or infection.
undul- wavy. Example: undulating, rising and falling, presenting a wavy appearance.
uni- one. Example: unicellular, pertaining to one cell.
vaccin- cow. Example: vaccination, injection of a vaccine (originally pertained to cows).
vacu- empty. Example: vacuoles, an intracellular space that appears empty.
vesic- bladder. Example: vesicle, a bubble.
vitr- glass. Example: in vitro, in culture media in a glass (or plastic) container.
-vorous eat. Example: carnivore, an animal that eats other animals.
xantho- yellow. Example: *Xanthomonas,* produces yellow colonies.
xeno- strange. Example: axenic, sterile, free of strange organisms.
xero- dry. Example: xerophyte, any plant that tolerates dry conditions.
xylo- wood. Example: xylose, a sugar obtained from wood.
zoo- animal. Example: zoology, the study of animals.
zygo- yoke, joining. Example: zygospore, a spore formed from the fusion of two cells.
-zyme ferment. Example: enzyme, any protein in living cells that catalyzes chemical reactions.

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Appendix F

Classification of Prokaryotes According to *Bergey's Manual*[*]

Domain: Archaea
- **Phylum Crenarchaeota**
  - Class: Thermoprotei
    - Order: Desulfurococcales
      - Family: Pyrodictiaceae
        - *Pyrodictium*
    - Order: Sulfolobales
      - Family: Sulfolobaceae
        - *Sulfolobus*
- **Phylum Euryarchaeota**
  - Class: Methanobacteria
    - Order: Methanobacteriales
      - Family: Methanobacteriaceae
        - *Methanobacterium*
      - Family: Methanosarcinaceae
        - *Methanosarcina*
  - Class: Methanococci
    - Order: Methanococcales
      - Family: Methaococcaceae
        - *Methanococcus*
        - *Methanothermococcus*
  - Class: Halobacteria
    - Order: Halobacteriales
      - Family: Halobacteriaceae
        - *Haloarcula*
        - *Halobacterium*
  - Class: Thermococci
    - Order: Thermococcales
      - Family: Thermococcaceae
        - *Pyrococcus*
        - *Thermococcus*

Domain: Bacteria
- Unclassified
  - *Thermovibrio*
- **Phylum Thermotogae**
  - Class: Thermotogae
    - Order: Thermotogales
      - Family: Thermotogaceae
        - *Thermotoga*
- **Phylum Deinococcus-Thermus**
  - Class: Deinococci
    - Order: Deinococcales
      - Family: Deinococcaceae
        - *Deinococcus*
    - Order: Thermales
      - *Thermus*
- **Phylum Chloroflexi**
  - Class: Chloroflexi
    - Order: Chloroflexales
      - Family: Chloroflexaceae
        - *Chloroflexus*
- **Phylum Cyanobacteria**
  - Class: Cyanobacteria
    - *Gloeocapsa*
    - *Prochlorococcus*
    - *Synechococcus*
    - *Spirulina*
    - *Anabaena*
- **Phylum Chlorobi**
  - Class: Chlorobia
    - Order: Chlorobiales
      - Family: Chlorobiaceae
        - *Chlorobium*

Phylum Proteobacteria
- Class: Alphaproteobacteria
  - Order: Rhodospirillales
    - Family: Rhodospirillaceae
      - *Azospirillum*
      - *Magnetospirillum*
      - *Rhodospirillum*
    - Family: Acetobacteraceae
      - *Acetobacter*
      - *Gluconacetobacter*
      - *Gluconobacter*
      - *Stella*
  - Order: Rickettsiales
    - Family: Rickettsiaceae
      - *Rickettsia*
    - Family: *Anaplasmataceae*
      - *Anaplasma*
      - *Ehrlichia*
      - *Wolbachia*
    - Unclassified
      - *Pelagibacter*
  - Order: Rhodobacterales
    - Family: Rhodobacteraceae
      - *Paracoccus*
  - Order: Caulobacterales
    - Family: Caulobacteraceae
      - *Caulobacter*
  - Order: Rhizobiales
    - Family: Rhizobiaceae
      - *Agrobacterium*
      - *Rhizobium*
    - Family: Bartonellaceae
      - *Bartonella*
    - Family: Brucellaceae
      - *Brucella*
    - Family: Beijerinckiaceae
      - *Beijerinckia*
    - Family: Bradyrhizobiaceae
      - *Bradyrhizobium*
      - *Nitrobacter*
      - *Rhodopseudomonas*
    - Family: Hyphomicrobiaceae
      - *Hyphomicrobium*
- Class: Betaproteobacteria
  - Order: Burkholderiales
    - Family: Burkholderiaceae
      - *Burkholderia*
      - *Cupriavidus*
      - *Ralstonia*
    - Family: Alcaligenaceae
      - *Bordetella*
    - Unclassified
      - *Sphaerotilus*
      - Order: Hydrogenophilales
    - Family: Hydrogenophilaceae
      - *Acidithiobacillus*
  - Order: Methylophilales
    - Family: Methylophilaceae
      - *Methylophilus*
  - Order: Neisseriales
    - Family: Neisseriaceae
      - *Neisseria*
  - Order: Nitrosomonadales
    - Family: Nitrosomonadaceae
      - *Nitrosomonas*
    - Family: Spirillaceae
      - *Spirillum*
  - Order: Rhodocyclales
    - Family: Rhodocyclaceae
      - *Zoogloea*
- Class: Gammaproteobacteria
  - Order: Chromatiales
    - Family: Chromatiaceae
      - *Chromatium*
    - Family: Ectothiorhodospiraceae
      - *Ectothiorhodospira*
  - Order: Xanthomonadales
    - Family: Xanthomonadaceae
      - *Xanthomonas*
  - Order: Thiotrichales
    - Family: Thiotrichaceae
      - *Beggiatoa*
      - *Thiomargarita*
    - Family: Francisellaceae
      - *Francisella*
  - Order: Legionellales
    - Family: Legionellaceae
      - *Legionella*
    - Family: Coxiellaceae
      - *Coxiella*
  - Order: Pseudomonadales
    - Family: Pseudomonadaceae
      - *Azomonas*
      - *Azotobacter*
      - *Pseudomonas*
    - Family: Moraxellaceae
      - *Acinetobacter*
      - *Moraxella*
  - Order: Vibrionales
    - Family: Vibrionaceae
      - *Aliivibrio*
      - *Photobacterium*
      - *Vibrio*
  - Order: Aeromonadales
    - Family: Aeromonadaceae
      - *Aeromonas*
  - Order: Enterobacteriales
    - Family: Enterobacteriaceae
      - *Citrobacter*
      - *Cronobacter*
      - *Enterobacter*
      - *Erwinia*
      - *Escherichia*
      - *Klebsiella*
      - *Pantoea*
      - *Plesiomonas*
      - *Proteus*
      - *Salmonella*
      - *Serratia*
      - *Shigella*
      - *Yersinia*
  - Order: Pasteurellales
    - Family: Pasteurellaceae
      - *Haemophilus*
      - *Pasteurella*
      - *Mannheimia*

[*] *Bergey's Manual of Systematic Bacteriology,* 2nd ed., 5 vols. (2004), is the reference for classification.*Bergey's Manual of Determinative Bacteriology,* 9th ed. (1994), should be used for identifying culturable bacteria and archaea.

- Unclassified
  - *Carsonella*
- Class: Deltaproteobacteria
  - Order: Desulfovibrionales
    - Family: Desulfovibrionaceae
      - *Desulfovibrio*
  - Order: Bdellovibrionales
    - Family: Bdellovibrionaceae
      - *Bdellovibrio*
  - Order: Myxococcales
    - Family: Myxococcaceae
      - *Myxococcus*
- Class: Epsilonproteobacteria
  - Order: Campylobacterales
    - Family: Campylobacteraceae
      - *Campylobacter*
    - Family: Helicobacteraceae
      - *Helicobacter*

Phylum Firmicutes

- Class: Bacilli
  - Order: Bacillales
    - Family: Bacillaceae
      - *Bacillus*
      - *Geobacillus*
    - Family: Listeriaceae
      - *Listeria*
    - Family: Paenibacillaceae
      - *Paenibacillus*
    - Family: Staphylococcaceae
      - *Staphylococcus*
    - Family: Thermoactinomycetaceae
      - *Thermoactinomyces*
  - Order: Lactobacillales
    - Family: Lactobacillaceae
      - *Lactobacillus*
      - *Pediococcus*
    - Family: Enterococcaceae
      - *Enterococcus*
    - Family: Leuconostocaceae
      - *Leuconostoc*
    - Family: Streptococcaceae
      - *Lactococcus*
      - *Streptococcus*
- Class: Clostridia
  - Order: Clostridiales
    - Family: Clostridiaceae
      - *Clostridium*
    - Family: Veillonellaceae
      - *Veillonella*
    - Unclassified
      - *Epulopiscium*
  - Order: Thermoanaerobacteriales
    - Family: Thermoanaerobacteriaceae
      - *Thermoanaerobacterium*

Phylum Tenericutes

- Order: Mycoplasmatales
  - Family: Mycoplasmataceae
    - *Mycoplasma*
    - *Ureaplasma*
  - Order: Entomoplasmatales
    - Family: Spiroplasmataceae
      - *Spiroplasma*
  - Order: Anaeroplasmatales
    - Family: Erysipelotrichidae
      - *Erysipelothrix*

Phylum Actinobacteria

- Class: Actinobacteria
  - Order: Actinomycetales
    - Family: Actinomycetaceae
      - *Actinomyces*
  - Suborder: Micrococcineae
    - Family: Micrococcaceae
      - *Micrococcus*
    - Family: Brevibacteriaceae
      - *Brevibacterium*
    - Family: Cellulomonadaceae
      - *Tropheryma*
    - Family: Corynebacteriaceae
      - *Corynebacterium*
    - Family: Mycobacteriaceae
      - *Mycobacterium*
    - Family: Nocardiaceae
      - *Nocardia*
      - *Rhodococcus*
    - Family: Micromonosporaceae
      - *Micromonospora*
    - Family: Propionibacteriaceae
      - *Propionibacterium*
    - Family: Streptomycetaceae
      - *Streptomyces*
    - Family: Frankiaceae
      - *Frankia*
  - Order: Bifidobacteriales
    - Family: Bifidobacteriaceae
      - *Bifidobacterium*
      - *Gardnerella*

Phylum Planctomycetes

- Order: Planctomycetales
  - Family: Planctomycetaceae
    - *Gemmata*
    - *Planctomyces*

Phylum Chlamydiae

- Order: Chlamydiales
  - Family: Chlamydiaceae
    - *Chlamydia*
    - *Chlamydophila*

Phylum Spirochaetes

- Class: Spirochaetes
  - Order: Spirochaetales
    - Family: Spirochaetaceae
      - *Borrelia*
      - *Treponema*
    - Family: Leptospiraceae
      - *Leptospira*

Phylum Bacteroidetes

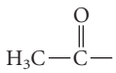
- Class: Bacteroidetes
  - Order: Bacteroidales
    - Family: Bacteroidaceae
      - *Bacteroides*
    - Family: Porphyromonadaceae
      - *Porphyromonas*
    - Family: Prevotellaceae
      - *Prevotella*
- Class: Flavobacteria
  - Family: Flavobacteriaceae
    - *Capnocytophaga*
- Class: Sphingobacteria
  - Order: Sphingobacteriales
    - Family: Flexibacteraceae
      - *Cytophaga*

Phylum Fusobacteria

- Class: Fusobacteria
  - Order: Fusobacteriales
    - Family: Fusobacteriaceae
      - *Fusobacterium*
      - *Streptobacillus*

Glossary

9 + 2 array Attachment of microtubules in eukaryotic flagella and cilia; 9 pairs of microtubules plus two microtubules.
12D treatment A sterilization process that would result in a decrease of the number of *Clostridium botulinum* endospores by 12 logarithmic cycles.

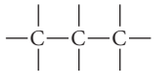
ABO blood group system The classification of red blood cells based on the presence or absence of A and B carbohydrate antigens.
abscess A localized accumulation of pus.
A-B toxin Bacterial exotoxins consisting of two polypeptides.
acellular vaccine A vaccine consisting of antigenic parts of cells.
acetyl group 
acid A substance that dissociates into one or more hydrogen ions (H^1) and one or more negative ions.
acid-fast stain A differential stain used to identify bacteria that are not decolorized by acid-alcohol.
acidic dye A salt in which the color is in the negative ion; used for negative staining.
acidophile A bacterium that grows below pH 4.
acquired immunodeficiency The inability, obtained during the life of an individual, to produce specific antibodies or T cells, due to drugs or disease.
activated macrophage A macrophage that has increased phagocytic ability and other functions after exposure to mediators released by T cells after stimulation by antigens.
activated sludge system A process used in secondary sewage treatment in which batches of sewage are held in highly aerated tanks; to ensure the presence of microbes efficient in degrading sewage, each batch is inoculated with portions of sludge from a precious batch.
activation energy The minimum collision energy required for a chemical reaction to occur.
active site A region on an enzyme that interacts with the substrate.
active transport Net movement of a substance across a membrane against a concentration gradient; requires the cell to expend energy.
acute disease A disease in which symptoms develop rapidly but last for only a short time.
acute-phase proteins Serum proteins whose concentration changes by at least 25% during inflammation.
adaptive immunity The ability, obtained during the life of the individual, to produce specific antibodies and T cells.
adenosarcoma Cancer of glandular epithelial tissue.
adenosine diphosphate (ADP) The substance formed when ATP is hydrolyzed and energy is released.
adenosine triphosphate (ATP) An important intracellular energy source.
adherence Attachment of a microbe or phagocyte to another's plasma membrane or other surface.
adhesin A carbohydrate-specific binding protein that projects from prokaryotic cells; used for adherence, also called a ligand.
adjuvant A substance added to a vaccine to increase its effectiveness.
aerobe An organism requiring molecular oxygen (O_2) for growth.
aerobic respiration Respiration in which the final electron acceptor in the electron transport chain is molecular oxygen (O_2).
aerotolerant anaerobe An organism that does not use molecular oxygen (O_2) but is not affected by its presence.
aflatoxin A carcinogenic toxin produced by *Aspergillus flavus*.
agar A complex polysaccharide derived from a marine alga and used as a solidifying agent in culture media.
agglutination A joining together or clumping of cells.
agranulocyte A leukocyte without visible granules in the cytoplasm when viewed through a light microscope; includes monocytes and lymphocytes.
alarmone A chemical signal that promotes a cell's response to environmental stress.
alcohol An organic molecule with the functional group—OH.
alcohol fermentation A catabolic process, beginning with glycolysis, that produces ethyl alcohol to reoxidize NADH.
aldehyde An organic molecule with the functional group 
alga (plural: algae) A photosynthetic eukaryote; may be unicellular, filamentous, or multicellular but lack the tissues found in plants.
algal bloom An abundant growth of microscopic algae producing visible colonies in nature.
algin A sodium salt of mannuronic acid ($C_6H_8O_6$); found in brown algae.
allergen An antigen that evokes a hypersensitivity response.
allergy *See* hypersensitivity.
allograft A tissue graft that is not from a genetically identical donor (i.e., not from self or an identical twin).
allosteric inhibition The process in which an enzyme's activity is changed because of binding to the allosteric site.
allosteric site The site on an enzyme at which a noncompetitive inhibitor binds.
allylamines Antifungal agents that interfere with sterol synthesis.
amanitin A polypeptide toxin produced by *Amanita* spp., inhibits RNA polymerase.
Ames test A procedure using bacteria to identify potential carcinogens.
amination The addition of an amino group.
amino acid An organic acid containing an amino group and a carboxyl group. In alpha-amino acids the amino and carboxyl groups are attached to the same carbon atom called the alpha-carbon.
aminoglycoside An antibiotic consisting of amino sugars and an aminocyclitol ring; for example, streptomycin.
amino group $—NH_2$.
ammonification The release of ammonia from nitrogen-containing organic matter by the action of microorganisms.
amphibolic pathway A pathway that is both anabolic and catabolic.
amphitrichous Having flagella at both ends of a cell.
anabolism All synthesis reactions in a living organism; the building of complex organic molecules from simpler ones.
anaerobe An organism that does not require molecular oxygen (O_2) for growth.
anaerobic respiration Respiration in which the final electron acceptor in the electron transport chain is an inorganic molecule other than molecular oxygen (O_2); for example, a nitrate ion or CO_2.
anaerobic sludge digester Anaerobic digestion used in secondary sewage treatment.
anal pore A site in certain protozoa for elimination of waste.
analytical epidemiology Comparison of a diseased group and a healthy group to determine the cause of the disease.
anamnestic response *See* memory response.
anamorph Ascomycete fungi that have lost the ability to reproduce sexually; the asexual stage of a fungus.
anaphylaxis A hypersensitivity reaction involving IgE antibodies, mast cells, and basophils.
Angstrom (Å) A unit of measurement equal to 10^{-10} m, or 0.1 nm.
Animalia The kingdom composed of multicellular eukaryotes lacking cell walls.
anion An ion with a negative charge.

anoxygenic Not producing molecular oxygen; typical of cyclic photophosphorylation.
antagonism Active opposition; (1) When two drugs are less effective than either one alone. (2) Competition among microbes.
antibiogram Report of antibiotic susceptibility of a bacterium.
antibiotic An antimicrobial agent, usually produced naturally by a bacterium or fungus.
antibody A protein produced by the body in response to an antigen, and capable of combining specifically with that antigen.
antibody-dependent cell-mediated cytotoxicity (ADCC) The killing of antibody-coated cells by natural killer cells and leukocytes.
antibody titer The amount of antibody in serum.
anticodon The three nucleotides by which a tRNA recognizes an mRNA codon.
antigen Any substance that causes antibody formation; also called an immunogen.
antigen–antibody complex The combination of an antigen with the antibody that is specific for it; the basis of immune protection and many diagnostic tests.
antigen-binding sites A site on an antibody that binds to an antigenic determinant.
antigenic determinant A specific region on the surface of an antigen against which antibodies are formed; also called epitope.
antigenic drift A minor variation in the antigenic makeup of influenza viruses that occurs with time.
antigenic shift A major genetic change in influenza viruses causing changes in H and N antigens.
antigenic variation Changes in surface antigens that occur in a microbial population.
antigen-presenting cell (APC) A macrophage, dendritic cell, or B cell that engulfs an antigen and presents fragments to T cells.
anti-human immune serum globulin (anti-HISG) An antibody that reacts specifically with human antibodies.
antimetabolite A competitive inhibitor.
antimicrobial peptide (AMP) An antibiotic that is bactericidal and has a broad spectrum of activity; *see* bacteriocin.
antisense DNA DNA that is complementary to the DNA encoding a protein; the antisense RNA transcript will hybridize with the mRNA encoding the protein and inhibit synthesis of the protein.
antisense strand (– strand) Viral RNA that cannot act as mRNA.
antisepsis A chemical method for disinfection of the skin or mucous membranes; the chemical is called an antiseptic.
antiserum A blood-derived fluid containing antibodies.
antitoxin A specific antibody produced by the body in response to a bacterial exotoxin or its toxoid.
antiviral protein (AVP) A protein made in response to interferon that blocks viral multiplication.
apoenzyme The protein portion of an enzyme, which requires activation by a coenzyme.
apoptosis The natural programmed death of a cell; the residual fragments are disposed of by phagocytosis.
aquatic microbiology The study of microorganisms and their activities in natural waters.
arbuscule Fungal mycelia in plant root cells.
archaea Domain of prokaryotic cells lacking peptidoglycan; one of the three domains.
arthroconidia An asexual fungal spore formed by fragmentation of a septate hypha.
Arthus reaction Inflammation and necrosis at the site of injection of foreign serum, due to immune complex formation.
artificially acquired active immunity The production of antibodies by the body in response to a vaccination.
artificially acquired passive immunity The transfer of humoral antibodies formed by one individual to a susceptible individual, accomplished by the injection of antiserum.
artificial selection Choosing one organism from a population to grow because of its desirable traits.
ascospore A sexual fungal spore produced in an ascus, formed by the ascomycetes.
ascus A saclike structure containing ascospores; found in the ascomycetes.
asepsis The absence of contamination by unwanted organisms.
aseptic packaging Commercial food preservation by filling sterile containers with sterile food.
aseptic surgery Techniques used in surgery to prevent microbial contamination of the patient.
aseptic techniques Laboratory techniques used to minimize contamination.
asexual spore A reproductive cell produced by mitosis and cell division (eukaryotes) or binary fission (actinomycetes).
atom The smallest unit of matter that can enter into a chemical reaction.
atomic force microscopy *See* scanned-probe microscopy.
atomic number The number of protons in the nucleus of an atom.
atomic weight The total number of protons and neutrons in the nucleus of an atom.
atrichous Bacteria that lack flagella.
attenuated vaccine A vaccine containing live, attenuated (weakened) microorganisms.
autoclave Equipment for sterilization by steam under pressure, usually operated at 15 psi and 121°C.
autograft A tissue graft from one's self.
autoimmune disease Damage to one's own organs due to action of the immune system.
autotroph An organism that uses carbon dioxide (CO_2) as its principal carbon source. chemoautotroph, photoautotroph.
auxotroph A mutant microorganism with a nutritional requirement that is absent in the parent.
axial filament The structure for motility found in spirochetes; also called endoflagellum.
azole Antifungal agents that interfere with sterol synthesis.

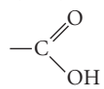
bacillus (plural: bacilli) (1) Any rod-shaped bacterium. (2) When written as a genus *(Bacillus)* refers to rod-shaped, endospore-forming, facultatively anaerobic, gram-positive bacteria.
bacteremia A condition in which there are bacteria in the blood.
bacteria Domain of prokaryotic organisms, characterized by peptidoglycan cell walls; **bacterium** (singular) when referring to a single organism.
bacterial growth curve A graph indicating the growth of a bacterial population over time.
bactericide A substance capable of killing bacteria.
bacteriocin An antimicrobial peptide produced by bacteria that kills other bacteria.
bacteriochlorophyll A photosynthetic pigment that transfers electrons for photophosphorylation; found in anoxygenic photosynthetic bacteria.
bacteriology The scientific study of prokaryotes, including bacteria and archaea.
bacteriophage (phage) A virus that infects bacterial cells.
bacteriostasis A treatment capable of inhibiting bacterial growth.
base A substance that dissociates into one or more hydroxide ions (OH^2) and one or more positive ions.
base pairs The arrangement of nitrogenous bases in nucleic acids based on hydrogen bonding; in DNA, base pairs are A-T and G-C; in RNA, base pairs are A-U and G-C.
base substitution The replacement of a single base in DNA by another base, causing a mutation; also called point mutation.
basic dye A salt in which the color is in the positive ion; used for bacterial stains.
basidiospore A sexual fungal spore produced in a basidium, characteristic of the basidiomycetes.
basidium A pedestal that produces basidiospores; found in the basidiomycetes.
basophil A granulocyte (leukocyte) that readily takes up basic dye and is not phagocytic; has receptors for IgE Fc regions.
batch production An industrial process in which cells are grown for a period of time after which the product is collected.
B cell A type of lymphocyte; differentiates into antibody-secreting plasma cells and memory cells.

BCG vaccine A live, attenuated strain of *Mycobacterium bovis* used to provide immunity to tuberculosis.
beer Alcoholic beverage produced by fermentation of starch.
benthic zone The sediment at the bottom of a body of water.
Bergey's Manual *Bergey's Manual of Systematic Bacteriology,* the standard taxonomic reference on bacteria; also refers to *Bergey's Manual of Determinative Bacteriology,* the standard laboratory identification reference on bacteria.
β-lactam Core structure of penicillins.
beta oxidation The removal of two carbon units from a fatty acid to form acetyl CoA.
binary fission Prokaryotic cell reproduction by division into two daughter cells.
binomial nomenclature The system of having two names (genus and specific epithet) for each organism; also called scientific nomenclature.
bioaugmentation The use of pollutant-acclimated microbes or genetically engineered microbes for bioremediation.
biochemical oxygen demand (BOD) A measure of the biologically degradable organic matter in water.
biocide A substance capable of killing microorganisms.
bioconversion Changes in organic matter brought about by the growth of microorganisms.
bioenhancer Nutrients such as nitrate and phosphate that promote microbial growth.
biofilm A microbial community that usually forms as a slimy layer on a surface.
biofuels Energy resources made by living organisms, usually from biomass, e.g., ethanol, methane.
biogenesis The theory that living cells arise only from preexisting cells.
biogeochemical cycle The recycling of chemical elements by microorganisms for use by other organisms.
bioinformatics The science of determining the function of genes through computer-assisted analysis.
biological transmission The transmission of a pathogen from one host to another when the pathogen reproduces in the vector.
bioluminescence The emission of light from the electron transport chain; requires the enzyme luciferase.
biomass Organic matter produced by living organisms and measured by weight.
bioreactor A fermentation vessel with controls for environmental conditions, e.g., temperature and pH.
bioremediation The use of microbes to remove an environmental pollutant.
Biosafety Level (BSL) Safety guidelines for working with live microorganisms in a laboratory, four levels called BSL-1 through BSL-4.
biosynthetic *See* anabolism.
biotechnology The industrial application of microorganisms, cells, or cell components to make a useful product.
bioterrorism Use of a living organism or its product to intimidate.
biotype *See* biovar.
biovar A subgroup of a serovar based on biochemical or physiological properties; also called biotype.
bioweapon Living organism or its product used to inflict harm.
bisphenol Phenolic that contains two phenol groups connected by a bridge.
blade A flat leaflike structure of multicellular algae.
blastoconidium An asexual fungal spore produced by budding from the parent cell.
blebbing Bulging of plasma membrane as a cell dies.
blood–brain barrier Cell membranes that allow some substances to pass from the blood to the brain but restrict others.
brightfield microscope A microscope that uses visible light for illumination; the specimens are viewed against a white background.
broad-spectrum antibiotic An antibiotic that is effective against a wide range of both gram-positive and gram-negative bacteria.
broth dilution test A method of determining the minimal inhibitory concentration by using serial dilutions of an antimicrobial drug.
bubo An enlarged lymph node caused by inflammation.
budding (1) Asexual reproduction beginning as a protuberance from the parent cell that grows to become a daughter cell. (2) Release of an enveloped virus through the plasma membrane of an animal cell.
budding yeast Following mitosis, a yeast cell that divides unevenly to produce a small cell (bud) from the parent cell.
buffer A substance that tends to stabilize the pH of a solution.
bulking A condition arising when sludge floats rather than settles in secondary sewage treatment.
bullae (singular: bulla) Large serum-filled vesicles in the skin.
bursa of Fabricius An organ in chickens responsible for maturation of the immune system.

Calvin-Benson cycle The fixation of CO_2 into reduced organic compounds; used by autotrophs.
capnophile A microorganism that grows best at relatively high CO_2 concentrations.
capsid The protein coat of a virus that surrounds the nucleic acid.
capsomere A protein subunit of a viral capsid.
capsule An outer, viscous covering on some bacteria composed of a polysaccharide or polypeptide.
carbapenems Antibiotics that contain a β-lactam antibiotic and cilastatin.
carbohydrate An organic compound composed of carbon, hydrogen, and oxygen, with the hydrogen and oxygen present in a 2:1 ratio; carbohydrates include starches, sugars, and cellulose.
carbon cycle The series of processes that converts CO_2 to organic substances and back to CO_2 in nature.
carbon fixation The synthesis of sugars by using carbons from CO_2. *See also* Calvin-Benson cycle.
carbon skeleton The basic chain or ring of carbon atoms in a molecule; for example,



carboxyl group



carboxysome A prokaryotic inclusion containing ribulose 1,5-diphosphate carboxylase.
carcinogen Any cancer-causing substance.
carrier Organism (usually refers to humans) that harbors pathogens and transmits them to others.
casein Milk protein.
catabolism All decomposition reactions in a living organism; the breakdown of complex organic compounds into simpler ones.
catabolite repression Inhibition of the metabolism of alternate carbon sources by glucose.
catalase An enzyme that breaks down hydrogen peroxide: $2H_2O_2 \rightarrow 2H_2O + O_2$
catalyst A substance that increases the rate of a chemical reaction but is not altered itself.
cation A positively charged ion.
CD (cluster of differentiation) Number assigned to an epitope on a single antigen, for example, CD4 protein, which is found on T helper cells.
cDNA (complementary DNA) DNA made in vitro from an mRNA template.
cell culture Eukaryotic cells grown in culture media; also called tissue culture.
cell theory All living organisms are composed of cells and arise from preexisting cells.
cellular immunity An immune response that involves T cells binding to antigens presented on antigen-presenting cells; T cells then differentiate into several types of effector T cells.
cellular respiration *See* respiration.
cell wall The outer covering of most bacterial, fungal, algal, and plant cells; in bacteria, it consists of peptidoglycan.
Centers for Disease Control and Prevention (CDC) A branch of the U.S. Public Health Service that serves a central source of epidemiological information.
central nervous system (CNS) The brain and the spinal cord. *See also* peripheral nervous system.

centriole A structure consisting of nine microtubule triplets, found in eukaryotic cells.
centrosome Region in a eukaryotic cell consisting of a pericentriolar area (protein fibers) and a pair of centrioles; involved in formation of the mitotic spindle.
cercaria A free-swimming larva of trematodes.
CFU (colony-forming unit) Visible bacterial colonies on solid media.
chancre A hard sore, the center of which ulcerates.
chemical bond An attractive force between atoms forming a molecule.
chemical element A fundamental substance composed of atoms that have the same atomic number and behave the same way chemically.
chemical energy The energy of a chemical reaction.
chemical reaction The process of making or breaking bonds between atoms.
chemically defined medium A culture medium in which the exact chemical composition is known.
chemiosmosis A mechanism that uses a proton gradient across a cytoplasmic membrane to generate ATP.
chemistry The science of the interactions between atoms and molecules.
chemoautotroph An organism that uses an inorganic chemical as an energy source and CO_2 as a carbon source.
chemoheterotroph An organism that uses organic molecules as a source of carbon and energy.
chemokine A cytokine that induces, by chemotaxis, the migration of leukocytes into infected areas.
chemotaxis Movement in response to the presence of a chemical.
chemotherapy Treatment of disease with chemical substances.
chemotroph An organism that uses oxidation-reduction reactions as its primary energy source.
chimeric monoclonal antibody A genetically engineered antibody made of human constant regions and mouse variable regions.
chlamydoconidium An asexual fungal spore formed within a hypha.
chlorophyll *a* A photosynthetic pigment that transfers electrons for photophosphorylation; found in plant, algae, and cyanobacteria.
chloroplast The organelle that performs photosynthesis in photoautotrophic eukaryotes.
chlorosome Plasma membrane folds in green sulfur bacteria containing bacteriochlorophylls.
chromatin Threadlike, uncondensed DNA in an interphase eukaryotic cell.
chromatophore An infolding in the plasma membrane where bacteriochlorophyll is located in photoautotrophic bacteria; also known as thylakoids.
chromosome The structure that carries hereditary information, chromosomes contain genes.
chronic infection An illness that develops slowly and is likely to continue or recur for long periods.
ciliary escalator Ciliated mucosal cells of the lower respiratory tract that move inhaled particulates away from the lungs.
cilium (plural: cilia) A relatively short cellular projection from some eukaryotic cells, composed of nine pairs plus two microtubules. *See* flagellum.
cis Hydrogen atoms on the same side across a double bond in a fatty acid. *See* trans.
cistern A flattened membranous sac in endoplasmic reticulum and the Golgi complex.
clade A group of organisms that share a particular common ancestor; a branch on a cladogram.
cladogram A dichotomous phylogenetic tree that branches repeatedly, suggesting the classification of organisms based on the time sequence in which evolutionary branches arose.
class A taxonomic group between phylum and order.
class switching Ability of a B cell to produce a different class of antibody against one antigen.
clonal deletion The elimination of B and T cells that react with self.
clonal selection The development of clones of B and T cells against a specific antigen.
clone A population of cells arising from a single parent cell.
clue cells Sloughed-off vaginal cells covered with *Gardnerella vaginalis*.
coagulase A bacterial enzyme that causes blood plasma to clot.
coccobacillus (plural: **coccobacilli**) A bacterium that is an oval rod.
coccus (plural: **cocci**) A spherical or ovoid bacterium.
codon A sequence of three nucleotides in mRNA that specifies the insertion of an amino acid into a polypeptide.
coenocytic hypha A fungal filament that is not divided into uninucleate cell-like units because it lacks septa.
coenzyme A nonprotein substance that is associated with and that activates an enzyme.
coenzyme A (CoA) A coenzyme that functions in decarboxylation.
coenzyme Q *See* ubiquinone.
cofactor (1) The nonprotein component of an enzyme. (2) A microorganism or molecule that acts with others to synergistically enhance or cause disease.
coliforms Aerobic or facultatively anaerobic, gram-negative, non–endospore-forming, rod-shaped bacteria that ferment lactose with acid and gas formation within 48 hours at 35°C.
collagenase An enzyme that hydrolyzes collagen.
collision theory The principle that chemical reactions occur because energy is gained as particles collide.
colony A visible mass of microbial cells arising from one cell or from a group of the same microbes.
colony hybridization The identification of a colony containing a desired gene by using a DNA probe that is complementary to that gene.
colony-stimulating factor (CSF) A substance that induces certain cells to proliferate or differentiate.
commensalism A symbiotic relationship in which two organisms live in association and one is benefited while the other is neither benefited nor harmed.
commercial sterilization A process of treating canned goods aimed at destroying the endospores of *Clostridium botulinum*.
communicable disease Any disease that can be spread from one host to another.
competence The physiological state in which a recipient cell can take and incorporate a large piece of donor DNA.
competitive exclusion Growth of some microbes prevents the growth of other microbes.
competitive inhibitor A chemical that competes with the normal substrate for the active site of an enzyme. *See also* noncompetitive inhibitor.
complement A group of serum proteins involved in phagocytosis and lysis of bacteria.
complementary DNA (cDNA) DNA made in vitro from an mRNA template.
complement fixation The process in which complement combines with an antigen–antibody complex.
complex medium A culture medium in which the exact chemical composition is not known.
complex virus A virus with a complicated structure, such as a bacteriophage.
composting A method of solid waste disposal, usually plant material, by encouraging its decomposition by microbes.
compound A substance composed of two or more different chemical elements.
compound light microscope (LM) An instrument with two sets of lenses that uses visible light as the source of illumination.
compromised host A host whose resistance to infection is impaired.
condensation reaction A chemical reaction in which a molecule of water is released; also called dehydration synthesis.
condenser A lens system located below the microscope stage that directs light rays through the specimen.
confocal microscopy A light microscope that uses fluorescent stains and laser to make two- and three-dimensional images.
congenital Refers to a condition existing at birth; may be inherited or acquired in utero.
congenital immunodeficiency The inability, due to an individual's genotype, to produce specific antibodies or T cells.
conidiophore An aerial hypha bearing conidiospores.
conidiospore *See* conidium.
conidium An asexual spore produced in a chain from a conidiophore.
conjugated monoclonal antibody *See* immunotoxin.

conjugated vaccine A vaccine consisting of the desired antigen and other proteins.
conjugation The transfer of genetic material from one cell to another involving cell-to-cell contact.
conjugative plasmid A prokaryotic plasmid that carries genes for sex pili and for transfer of the plasmid to another cell.
constitutive enzyme An enzyme that is produced continuously.
contact inhibition The cessation of animal cell movement and division as a result of contact with other cells.
contact transmission The spread of disease by direct or indirect contact or via droplets.
contagious disease A disease that is easily spread from one person to another.
continuous cell line Animal cells that can be maintained through an indefinite number of generations in vitro.
continuous flow An industrial fermentation in which cells are grown indefinitely with continual addition of nutrients and removal of waste and products.
corepressor A molecule that binds to a repressor protein, enabling the repressor to bind to an operator.
cortex The protective fungal covering of a lichen.
counterstain A second stain applied to a smear, provides contrast to the primary stain.
covalent bond A chemical bond in which the electrons of one atom are shared with another atom.
crisis The phase of a fever characterized by vasodilation and sweating.
crista (plural: cristae) Folding of the inner membrane of a mitochondrion.
crossing over The process by which a portion of one chromosome is exchanged with a portion of another chromosome.
CTL (cytotoxic T lymphocyte) An activated $CD8^+$ T cell; kills cells presenting endogenous antigens.
culture Microorganisms that grow and multiply in a container of culture medium.
culture medium The nutrient material prepared for growth of microorganisms in a laboratory.
curd The solid part of milk that separates from the liquid (whey) in the making of cheese, for example.
cutaneous mycosis A fungal infection of the epidermis, nails, or hair.
cuticle The outer covering of helminths.
cyanobacteria Oxygen-producing photoautotrophic prokaryotes.
cyclic AMP (cAMP) A molecule derived from ATP, in which the phosphate group has a cyclic structure; acts as a cellular messenger.
cyclic photophosphorylation The movement of an electron from chlorophyll through a series of electron acceptors and back to chlorophyll; anoxygenic; purple and green bacterial photophosphorylation.
cyst A sac with a distinct wall containing fluid or other material; also, a protective capsule of some protozoa.
cysticercus An encysted tapeworm larva.
cytochrome A protein that functions as an electron carrier in cellular respiration and photosynthesis.
cytochrome c oxidase An enzyme that oxidizes cytochrome *c*.
cytokine A small protein released from human cells that regulates the immune response; directly or indirectly may induce fever, pain, or T cell proliferation.
cytokine storm Overproduction of cytokines; can cause damage to the human body.
cytolysis The destruction of cells, resulting from damage to their cell membrane, that causes cellular contents to leak out.
cytopathic effect (CPE) A visible effect on a host cell, caused by a virus, that may result in host cell damage or death.
cytoplasm In a prokaryotic cell, everything inside the plasma membrane; in a eukaryotic cell, everything inside the plasma membrane and external to the nucleus.
cytoplasmic streaming The movement of cytoplasm in a eukaryotic cell.
cytoskeleton Microfilaments, intermediate filaments, and microtubules that provide support and movement for eukaryotic cytoplasm.
cytosol The fluid portion of cytoplasm.
cytostome The mouthlike opening in some protozoa.
cytotoxin A bacterial toxin that kills host cells or alters their functions.

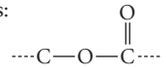
darkfield microscope A microscope that has a device to scatter light from the illuminator so that the specimen appears white against a black background.
deamination The removal of an amino group from an amino acid to form ammonia. *See also* ammonification.
death phase The period of logarithmic decrease in a bacterial population; also called logarithmic decline phase.
debridement Surgical removal of necrotic tissue.
decarboxylation The removal of CO_2 from an amino acid.
decimal reduction time (DRT) The time (in minutes) required to kill 90% of a bacterial population at a given temperature; also called D value.
decolorizing agent A solution used in the process of removing a stain.
decomposition reaction A chemical reaction in which bonds are broken to produce smaller parts from a large molecule.
deep-freezing Preservation of bacterial cultures at 250°C to 295°C.
defensins Small peptide antibiotics made by human cells.
definitive host An organism that harbors the adult, sexually mature form of a parasite.
degeneracy Redundancy of the genetic code; that is, most amino acids are encoded by several codons.
degerming The removal of microorganisms in an area; also called degermation.
degranulation The release of contents of secretory granules from mast cells or basophils during anaphylaxis.
dehydration synthesis *See* condensation reaction.
dehydrogenation The loss of hydrogen atoms from a substrate.
delayed hypersensitivity Cell-mediated hypersensitivity.
denaturation A change in the molecular structure of a protein, usually making it nonfunctional.
dendritic cell (DC) A type of antigen-presenting cell characterized by long finger like extensions; found in lymphatic tissue and skin.
denitrification The reduction of nitrogen in nitrate to nitrite or nitrogen gas.
dental plaque A combination of bacterial cells, dextran, and debris adhering to the teeth.
deoxyribonucleic acid (DNA) The nucleic acid of genetic material in all cells and some viruses.
deoxyribose A five-carbon sugar contained in DNA nucleotides.
dermatomycosis A fungal infection of the skin; also known as tinea or ringworm.
dermatophyte A fungus that causes a cutaneous mycosis.
dermis The inner portion of the skin.
descriptive epidemiology The collection and analysis of all data regarding the occurrence of a disease to determine its cause.
desensitization The prevention of allergic inflammatory responses.
desiccation The removal of water.
diapedesis The process by which phagocytes move out of blood vessels.
dichotomous key An identification scheme based on successive paired questions; answering one question leads to another pair of questions, until an organism is identified.
differential interference contrast (DIC) microscope An instrument that provides a three-dimensional, magnified image.
differential medium A solid culture medium that makes it easier to distinguish colonies of the desired organism.
differential stain A stain that distinguishes objects on the basis of reactions to the staining procedure.
differential white blood cell count The number of each kind of leukocyte in a sample of 100 leukocytes.
diffusion The net movement of molecules or ions from an area of higher concentration to an area of lower concentration.
dimorphism The property of having two forms of growth. *See also* sexual dimorphism.
dioecious Referring to organisms in which organs of different sexes are located in different individuals.
diplobacilli (singular: **diplobacillus**) Rods that divide and remain attached in pairs.

diplococci (singular: **diplococcus**) Cocci that divide and remain attached in pairs.
diploid cell A cell having two sets of chromosomes; diploid is the normal state of a eukaryotic cell.
diploid cell line Eukaryotic cells grown in vitro.
direct agglutination test The use of known antibodies to identify an unknown cell-bound antigen.
direct contact transmission A method of spreading infection from one host to another through some kind of close association between the hosts.
direct fluorescent-antibody (DFA) test A fluorescent-antibody test to detect the presence of an antigen.
direct microscopic count Enumeration of cells by observation through a microscope.
disaccharide A sugar consisting of two simple sugars, or monosaccharides.
disease An abnormal state in which part or all of the body is not properly adjusted or is incapable of performing normal functions; any change from a state of health.
disinfection Any treatment used on inanimate objects to kill or inhibit the growth of microorganisms; a chemical used is called a disinfectant.
disk-diffusion method An agar-diffusion test to determine microbial susceptibility to chemotherapeutic agents; also called Kirby-Bauer test.
D-isomer Arrangement of four different atoms or groups around a carbon atom. *See* L-isomer.
dissimilation A metabolic process in which nutrients are not assimilated but are excreted as ammonia, hydrogen sulfide, and so on.
dissimilation plasmid A plasmid containing genes encoding production of enzymes that trigger the catabolism of certain unusual sugars and hydrocarbons.
dissociation The separation of a compound into positive and negative ions in solution. *See also* ionization.
disulfide bond A covalent bond that holds together two atoms of sulfur.
DNA base composition The moles-percentage of guanine plus cytosine in an organism's DNA.
DNA chip ("microarray") A silica wafer that holds DNA probes; used to recognize DNA in samples being tested.
DNA fingerprinting Analysis of DNA by electrophoresis of restriction enzyme fragments of the DNA.
DNA gyrase *See* topoisomerase.
DNA ligase An enzyme that covalently bonds a carbon atom of one nucleotide with the phosphate of another nucleotide.
DNA polymerase Enzyme that synthesizes DNA by copying a DNA template.
DNA probe A short, labeled, single strand of DNA or RNA used to locate its complementary strand in a quantity of DNA.
DNA sequencing A process by which the nucleotide sequence of DNA is determined.
domain A taxonomic classification based on rRNA sequences; above the kingdom level.
donor cell A cell that gives DNA to a recipient cell during genetic recombination.
droplet transmission The transmission of infection by small liquid droplets carrying microorganisms.
DTaP vaccine A combined vaccine used to provide active immunity, containing diphtheria and tetanus toxoids and *Bordetella pertussis* cell fragments.
D value *See* decimal reduction time.
dysentery A disease characterized by frequent, watery stools containing blood and mucus.

eclipse period The time during viral multiplication when complete, infective virions are not present.
ecology The study of the interrelationships between organisms and their environment.
edema An abnormal accumulation of interstitial fluid in tissues, causing swelling.
electron A negatively charged particle in motion around the nucleus of an atom.
electron acceptor An ion that picks up an electron that has been lost from another atom.
electron donor An ion that gives up an electron to another atom.
electronic configuration The arrangement of electrons in shells or energy levels in an atom.
electron microscope A microscope that uses electrons instead of light to produce an image.
electron shell A region of an atom where electrons orbit the nucleus, corresponding to an energy level.
electron transport chain, electron transport system A series of compounds that transfer electrons from one compound to another, generating ATP by oxidative phosphorylation.
electroporation A technique by which DNA is inserted into a cell using an electrical current.
elementary body The infectious form of chlamydiae.
ELISA (enzyme-linked immunosorbent assay) A group of serological tests that use enzyme reactions as indicators.
embryonic stem cell (ESC) A cell from an embryo that has the potential to become a wide variety of specialized cell types.
emerging infectious disease (EID) A new or changing disease that is increasing or has the potential to increase in incidence in the near future.
Embden-Meyerhof pathway *See* glycolysis.
enanthem Rash on mucous membranes. *See also* exanthem.
encephalitis Infection of the brain.
encystment Formation of a cyst.
endemic disease A disease that is constantly present in a certain population.
endergonic reaction A chemical reaction that requires energy.
endocarditis Infection of the lining of the heart (endocardium).
endocytosis The process by which material is moved into a eukaryotic cell.
endoflagellum *See* axial filament.
endogenous (1) Infection caused by an opportunistic pathogen from an individual's own normal microbiota. (2) Surface antigens on human cells produced as a result of infection.
endolith An organism that lives inside rock.
endoplasmic reticulum (ER) A membranous network in eukaryotic cells connecting the plasma membrane with the nuclear membrane.
endospore A resting structure formed inside some bacteria.
endosymbiotic theory A model for the evolution of eukaryotes which states that organelles arose from prokaryotic cells living inside a host prokaryote.
endotoxic shock *See* gram-negative sepsis.
endotoxin Part of the outer portion of the cell wall (lipid A) of most gram-negative bacteria; released on destruction of the cell.
end-product inhibition *See* feedback inhibition.
energy level Potential energy of an electron in an atom. *See also* electron shell.
enrichment culture A culture medium used for preliminary isolation that favors the growth of a particular microorganism.
enteric The common name for a bacterium in the family Enterobacteriaceae.
enterotoxin An exotoxin that causes gastroenteritis, such as those produced by *Staphylococcus, Vibrio,* and *Escherichia*.
Entner-Doudoroff pathway An alternate pathway for the oxidation of glucose to pyruvic acid.
envelope An outer covering surrounding the capsid of some viruses.
enzyme A molecule that catalyzes biochemical reactions in a living organism, usually a protein. *See also* ribozyme.
enzyme immunoassay (EIA) *See* ELISA
enzyme-linked immunosorbent assay *See* ELISA.
enzyme–substrate complex A temporary union of an enzyme and its substrate.
eosinophil A granulocyte whose granules take up the stain eosin.
epidemic disease A disease acquired by many hosts in a given area in a short time.
epidemiology The science that studies when and where diseases occur and how they are transmitted.
epidermis The outer portion of the skin.
epitope *See* antigenic determinant.
equilibrium The point of even distribution.
equivalent treatments Different methods that have the same effect on controlling microbial growth.

ergot A toxin produced in sclerotia by the fungus *Claviceps purpurea* that causes ergotism.

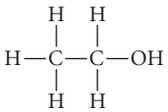
ester linkage Bonding between fatty acids and glycerol in bacterial and eukaryotic phospholipids:



E test An agar diffusion test to determine antibiotic sensitivity using a plastic strip impregnated with varying concentrations of an antibiotic.

ethambutol A synthetic antimicrobial agent that interferes with the synthesis of RNA.

ethanol



ether linkage Bonding between fatty acids and glycerol in archaeal phospholipids: -----C—O—C-----

etiology The study of the cause of a disease.

eukarya All eukaryotes (animals, plants, fungi, and protists); members of the Domain Eukarya.

eukaryote A cell having DNA inside a distinct membrane-enclosed nucleus.

eukaryotic species A group of closely related organisms that can interbreed.

eutrophication The addition of organic matter and subsequent removal of oxygen from a body of water.

exanthem Skin rash. *See also* enanthem.

exchange reaction A chemical reaction that has both synthesis and decomposition components.

exergonic reaction A chemical reaction that releases energy.

exon A region of a eukaryotic chromosome that encodes a protein.

exotoxin A protein toxin released from living, mostly gram-positive bacterial cells.

experimental epidemiology The study of a disease using controlled experiments.

exponential growth phase *See* log phase.

extracellular polymeric substance (EPS) A glycocalyx that permits bacteria to attach to various surfaces.

extreme thermophile *See* hyperthermophile.

extremophile A microorganism that lives in environmental extremes of temperature, acidity, alkalinity, salinity, or pressure.

extremozymes Enzymes produced by extremophiles.

facilitated diffusion The movement of a substance across a plasma membrane from an area of higher concentration to an area of lower concentration, mediated by transporter proteins.

facultative anaerobe An organism that can grow with or without molecular oxygen (O_2).

facultative halophile An organism capable of growth in, but not requiring, 1–2% salt.

FAD Flavin adenine dinucleotide; a coenzyme that functions in the removal and transfer of hydrogen ions (H^1) and electrons from substrate molecules.

FAME Fatty acid methyl ester; identification of microbes by the presence of specific fatty acids.

family A taxonomic group between order and genus.

feedback inhibition Inhibition of an enzyme in a particular pathway by the accumulation of the end-product of the pathway; also called end-product inhibition.

fermentation The enzymatic degradation of carbohydrates in which the final electron acceptor is an organic molecule, ATP is synthesized by substrate-level phosphorylation, and O_2 is not required.

fermentation test Method used to determine whether a bacterium or yeast ferments a specific carbohydrate; usually performed in a peptone broth containing the carbohydrate, a pH indicator, and an inverted tube to trap gas.

fever An abnormally high body temperature.

F factor (fertility factor) A plasmid found in the donor cell in bacterial conjugation.

fibrinolysin A kinase produced by streptococci.

filtration The passage of a liquid or gas through a screenlike material; a 0.45-µm filter removes most bacteria.

fimbria (plural: fimbriae) An appendage on a bacterial cell used for attachment.

FISH Fluorescent in situ hybridization; use of rRNA probes to identify microbes without cutturing.

fission yeast Following mitosis, a yeast cell that divides evenly to produce two new cells.

fixed macrophage A macrophage that is located in a certain organ or tissue (e.g., liver, lungs, spleen, or lymph nodes); also called a histiocyte.

fixing (1) In slide preparation, the process of attaching a specimen to a slide. (2) Regarding chemical elements, combining elements so that a critical element can enter the food chain. *See also* Calvin-Benson cycle; nitrogen fixation.

flaccid paralysis Loss of muscle movement, loss of muscle tone.

flagellum (plural: flagella) A thin appendage from the surface of a cell; used for cellular locomotion; composed of flagellin in prokaryotic cells, composed of 9 1 2 microtubules in eukaryotic cells.

flaming The process of sterilizing an inoculating loop by holding it in an open flame.

flat sour spoilage Thermophilic spoilage of canned goods not accompanied by gas production.

flatworm An animal belonging to the phylum Platyhelminthes.

flavoprotein A protein containing the coenzyme flavin; functions as an electron carrier in electron transport chains.

flocculation The removal of colloidal material during water purification by adding a chemical that causes colloidal particles to coalesce.

flow cytometry A method of counting cells using a flow cytometer, which detects cells by the presence of a fluorescent tag on the cell surface.

fluid mosaic model A way of describing the dynamic arrangement of phospholipids and proteins comprising the plasma membrane.

fluke A flatworm belonging to the class Trematoda.

fluorescence The ability of a substance to give off light of one color when exposed to light of another color.

fluorescence-activated cell sorter (FACS) A modification of a flow cytometer that counts and sorts cells labeled with fluorescent antibodies.

fluorescence microscope A microscope that uses an ultraviolet light source to illuminate specimens that will fluoresce.

fluorescent-antibody (FA) technique A diagnostic tool using antibodies labeled with fluorochromes and viewed through a fluorescence microscope; also called immunofluorescence.

FMN Flavin mononucleotide; a coenzyme that functions in the transfer of electrons in the electron transport chain.

focal infection A systemic infection that began as an infection in one place.

folliculitis An infection of hair follicles, often occurring as pimples.

fomite A nonliving object that can spread infection.

forespore A structure consisting of chromosome, cytoplasm, and endospore membrane inside a bacterial cell.

frameshift mutation A mutation caused by the addition or deletion of one or more bases in DNA.

free radical A compound with an unpaired electron. *See* superoxide.

free (wandering) macrophage A macrophage that leaves the blood and migrates to infected tissue.

freeze-drying *See* lyophilization.

FTA-ABS test An indirect fluorescent-antibody test used to detect syphilis.

fulminating A condition that develops quickly and rapidly increases in severity.

functional group An arrangement of atoms in an organic molecule that is responsible for most of the chemical properties of that molecule.

fungus (plural: **fungi**) An organism that belongs to the Kingdom Fungi; a eukaryotic absorptive chemoheterotroph.

furuncle An infection of a hair follicle.

fusion The merging of plasma membranes of two different cells, resulting in one cell containing cytoplasm from both original cells.

gamete A male or female reproductive cell.

gametocyte A male or female protozoan cell.

gamma globulin The serum fraction containing immunoglobulins (antibodies); also called immune serum globulin.

gastroenteritis Inflammation of the stomach and intestine.

gas vacuole A prokaryotic inclusion for buoyancy compensation.
gel electrophoresis The separation of substances (such as serum proteins or DNA) by their rate of movement through an electrical field.
gene A segment of DNA (a sequence of nucleotides in DNA) encoding a functional product.
gene silencing A mechanism to inhibit gene expression. *See* RNAi.
gene therapy Treating a disease by replacing abnormal genes.
generalized transduction The transfer of bacterial chromosome fragments from one cell to another by a bacteriophage.
generation time The time required for a cell or population to double in number.
genetic code The mRNA codons and the amino acids they encode.
genetic engineering *See* recombinant DNA technology.
genetic recombination The process of joining pieces of DNA from different sources.
genetics The science of heredity and gene function.
genetic testing Techniques for determining which genes are in a cell's genome.
genome One complete copy of the genetic information in a cell.
genomic library A collection of cloned DNA fragments created by inserting restriction enzyme fragments in a bacterium, yeast, or phage.
genomics The study of genes and their function.
genotype The genetic makeup of an organism.
genus (plural: genera) The first name of the scientific name (binomial); the taxon between family and species.
germicide *See* biocide.
germination The process of starting to grow from a spore or endospore.
germ theory of disease The principle that microorganisms cause disease.
global warming Retention of solar heat by gases in the atmosphere.
globulin The class of globular proteins that includes antibodies. *See also* immunoglobulin.
glycocalyx A gelatinous polymer surrounding a cell.
glycolysis The main pathway for the oxidation of glucose to pyruvic acid; also called Embden-Meyerhof pathway.
Golgi complex An organelle involved in the secretion of certain proteins.
graft-versus-host (GVH) disease A condition that occurs when a transplanted tissue has an immune response to the tissue recipient.
gram-negative bacteria Bacteria that lose the crystal violet color after decolorizing by alcohol; they stain red after treatment with safranin.
gram-negative sepsis Septic shock caused by gram-negative endotoxins.
gram-positive bacteria Bacteria that retain the crystal violet color after decolorizing by alcohol; they stain dark purple.
gram-positive sepsis Septic shock caused by gram-positive bacteria.
Gram stain A differential stain that classifies bacteria into two groups, gram-positive and gram-negative.
granulocyte A leukocyte with visible granules in the cytoplasm when viewed through a light microscope; includes neutrophils, basophils, and eosinophils.
granuloma A lump of inflamed tissue containing macrophages.
granum (plural: **grana**) Stack of thylakoid membrane.
granzymes Proteases that induce apoptosis.
green nonsulfur bacteria Gram-negative, nonproteobacteria; anaerobic and phototrophic; use reduced organic compounds as electron donors for CO_2 fixation.
green sulfur bacteria Gram-negative, nonproteobacteria; strictly anaerobic and phototrophic; no growth in dark; use reduced sulfur compounds as electron donors for CO_2 fixation.
group translocation In prokaryotes, active transport in which a substance is chemically altered during transport across the plasma membrane.
gumma A rubbery mass of tissue characteristic of tertiary syphilis.

HAART (highly active antiretroviral therapy) A combination of drugs used to treat HIV infection.
halogen One of the following elements: fluorine, chlorine, bromine, iodine, or astatine.
halophile An organism that requires a high salt concentration for growth.
H antigen Flagella antigens of enterics, identified by serological testing.
haploid cell A eukaryotic cell or organism with one of each type of chromosome.
hapten A substance of low molecular weight that does not cause the formation of antibodies by itself but does so when combined with a carrier molecule.
HA (hemagglutinin) spike Antigenic projections from the outer lipid bilayer of *Influenzavirus*.
Hazard Analysis and Critical Control Point (HACCP) System of prevention of hazards, for food safety.
healthcare-associated infection (HAI) An infection that develops during a stay at a health care facility and was not present at the time the patient was admitted.
helminth A parasitic roundworm or flatworm.
hemagglutination The clumping of red blood cells.
hematopoiesis The formation of blood cells.
hemoflagellate A parasitic flagellate found in the circulatory system of its host.
hemolysin An enzyme that lyses red blood cells.
herd immunity The presence of immunity in most of a population.
hermaphroditic Having both male and female reproductive capacities.
heterocyst A large cell in certain cyanobacteria; the site of nitrogen fixation.
heterolactic Describing an organism that produces lactic acid and other acids or alcohols as end-products of fermentation; e.g., *Escherichia*.
heterotroph An organism that requires an organic carbon source; also called organotroph.
Hfr cell A bacterial cell in which the F factor has become integrated into the chromosome; Hfr stands for high frequency of recombination.
high-efficiency particulate air (HEPA) filter A screenlike material that removes particles larger than 0.3 μm from air.
high-temperature short-time (HTST) pasteurization Pasteurizing at 72°C for 15 seconds.
histamine A substance released by tissue cells that causes vasodilation, capillary permeability, and smooth muscle contraction.
histocompatibility antigen An antigen on the surface of human cells.
histone A protein associated with DNA in eukaryotic chromosomes.
holdfast The branched base of an algal stipe.
holoenzyme An enzyme consisting of an apoenzyme and a cofactor.
homolactic Describing an organism that produces only lactic acid from fermentation; e.g., *Streptococcus*.
horizontal gene transfer Transfer of genes between two organisms in the same generation. *See also* vertical gene transfer.
host An organism infected by a pathogen. *See also* definitive host; intermediate host.
host range The spectrum of species, strains, or cell types that a pathogen can infect.
hot-air sterilization Sterilization by the use of an oven at 170°C for approximately 2 hours.
human leukocyte antigen (HLA) complex Human cell surface antigens. *See also* major histocompatibility complex.
Human Microbiome Project A project to characterize the microbial communities found on the human body.
humanized antibody Human antibodies produced by genetically modified mice.
humoral immunity Immunity produced by antibodies dissolved in body fluids, mediated by B cells; also called antibody-mediated immunity.
hyaluronidase An enzyme secreted by certain bacteria that hydrolyzes hyaluronic acid and helps spread microorganisms from their initial site of infection.
hybridoma A cell made by fusing an antibody-producing B cell with a cancer cell.
hydrogen bond A bond between a hydrogen atom covalently bonded to oxygen or nitrogen and another covalently bonded oxygen or nitrogen atom.
hydrolysis A decomposition reaction in which chemicals react with the H^+ and OH^- of a water molecule.
hydroxide OH^-; the anion that forms a base.
hydroxyl —OH; covalently bonded to a molecule forms an alcohol.
hydroxyl radical A toxic form of oxygen (OH•) formed in cytoplasm by ionizing radiation and aerobic respiration.
hyperacute rejection Very rapid rejection of transplanted tissue, usually in the case of tissue from nonhuman sources.

hyperbaric chamber An apparatus to hold materials at pressures greater than 1 atmosphere.
hypersensitivity An altered, enhanced immune reaction leading to pathological changes; also called allergy.
hyperthermophile An organism whose optimum growth temperature is at least 80°C; also called extreme thermophile.
hypertonic solution A solution that has a higher concentration of solutes than an isotonic solution.
hypha A long filament of cells in fungi or actinomycetes.
hypotonic solution A solution that has a lower concentration of solutes than an isotonic solution.

ID_{50} The number of microorganisms required to produce a demonstrable infection in 50% of the test host population.
idiophase The period in the production curve of an industrial cell population in which secondary metabolites are produced; a period of stationary growth following the phase of rapid growth. *See also* trophophase.
IgA The class of antibodies found in secretions.
IgD The class of antibodies found on B cells.
IgE The class of antibodies involved in hypersensitivities.
IgG The most abundant class of antibodies in serum.
IgM The first class of antibodies to appear after exposure to an antigen.
immune complex A circulating antigen-antibody aggregate capable of fixing complement.
immune serum globulin *See* gamma globulin.
immune surveillance The body's immune response to cancer.
immunity *See* adaptive immunity, innate immunity.
immunization *See* vaccination.
immunodeficiency The absence of an adequate immune response; may be congenital or acquired.
immunodiffusion test A test consisting of precipitation reactions carried out in an agar gel medium.
immunoelectrophoresis The identification of proteins by electrophoretic separation followed by serological testing.
immunofluorescence *See* fluorescent-antibody technique.
immunogen *See* antigen.
immunoglobulin (Ig) A protein (antibody) formed in response to an antigen and can react with that antigen. *See also* globulin.
immunology The study of a host's defenses to a pathogen.
immunosuppression Inhibition of the immune response.
immunotherapy Making use of the immune system to attack tumor cells, either by enhancing the normal immune response or by using toxin-bearing specific antibodies. *See also* immunotoxin.
immunotoxin An immunotherapeutic agent consisting of a poison bound to a monoclonal antibody.
inapparent infection *See* subclinical infection.
incidence The fraction of the population that contracts a disease during a particular period of time.
inclusion Material held inside a cell, often consisting of reserve deposits.
inclusion body A granule or viral particle in the cytoplasm or nucleus of some infected cells; important in the identification of viruses that cause infection.
incubation period The time interval between the actual infection and first appearance of any signs or symptoms of disease.
indicator organism A microorganism, such as a coliform, whose presence indicates conditions such as fecal contamination of food or water.
indirect (passive) agglutination test An agglutination test using soluble antigens attached to latex or other small particles.
indirect contact transmission The spread of pathogens by fomites (nonliving objects).
indirect FA test A fluorescent-antibody test to detect the presence of specific antibodies.
inducer A chemical or environmental stimulus that causes transcription of specific genes.
induction The process that turns on the transcription of a gene.
infection The growth of microorganisms in the body.
infectious disease A disease in which pathogens invade a susceptible host and carry out at least part of their life cycle in the host.
inflammation A host response to tissue damage characterized by redness, pain, heat, and swelling; and sometimes loss of function.
innate immunity Host defenses that afford protection against any kind of pathogen. *See also* adaptive immunity.
inoculum Microbes introduced into a culture medium to initiate growth.
inorganic compound A small molecule that does not contain carbon and hydrogen.
insertion sequence (IS) The simplest kind of transposon.
integrase An enzyme produced by HIV that allows the integration of HIV DNA into the host cell's DNA.
interferon (IFN) A specific group of cytokines. Alpha- and beta-IFNs are antiviral proteins produced by certain animal cells in response to a viral infection. Gamma-IFN stimulates macrophage activity.
interleukin (IL) A chemical that causes T-cell proliferation. *See also* cytokine.
intermediate host An organism that harbors the larval or asexual stage of a helminth or protozoan.
intoxication A condition resulting from the ingestion of a microbially produced toxin.
intron A region in a eukaryotic gene that does not code for a protein or mRNA.
intubation Placing a tube into the body; tracheal intubation provides access for air to the lungs.
invasin A surface protein produced by *Salmonella typhimurium* and *Escherichia coli* that rearranges nearby actin filaments in the cytoskeleton of a host cell.
iodophor A complex of iodine and a detergent.
ion A negatively or positively charged atom or group of atoms.
ionic bond A chemical bond formed when atoms gain or lose electrons in the outer energy levels.
ionization The separation (dissociation) of a molecule into ions.
ionizing radiation High-energy radiation with a wavelength less than 1nm; causes ionization. X rays and gamma rays are examples.
ischemia Localized decreased blood flow.
isograft A tissue graft from a genetically identical source (i.e., from an identical twin).
isomer One or two molecules with the same chemical formula but different structures.
isotonic solution A solution in which, after immersion of a cell, osmotic pressure is equal across the cell's membrane.
isotope A form of a chemical element in which the number of neutrons in the nucleus is different from the other forms of that element.

karyogamy Fusion of the nuclei of two cells; occurs in the sexual stage of a fungal life cycle.
kelp A multicellular brown alga.
keratin A protein found in epidermis, hair, and nails.
ketolide Semisynthetic macrolide antibiotic; effective against macrolide-resistant bacteria
kinase (1) An enzyme that removes a P from ATP and attaches it to another molecule. (2) A bacterial enzyme that breaks down fibrin (blood clots).
kingdom A taxonomic classification between domain and phylum.
kinin A substance released from tissue cells that causes vasodilation.
Kirby-Bauer test *See* disk-diffusion method.
Koch's postulates Criteria used to determine the causative agent of infectious diseases.
koji A microbial fermentation on rice; usually *Aspergillus oryzae;* used to produce amylase.
Krebs cycle A pathway that converts two-carbon compounds to CO_2, transferring electrons to NAD^+ and other carriers; also called tricarboxylic acid (TCA) cycle or critic acid cycle.

lactic acid fermentation A catabolic process, beginning with glycolysis, that produces lactic acid to reoxidize NADH.
lagging strand During DNA replication, the daughter strand that is synthesized discontinuously.
lag phase The time interval in a bacterial growth curve during which there is no growth.
larva The sexually immature stage of a helminth or arthropod.

latent disease A disease characterized by a period of no symptoms when the pathogen is inactive.
latent infection A condition in which a pathogen remains in the host for long periods without producing disease.
LD_{50} The lethal dose for 50% of the inoculated hosts within a given period.
leading strand During DNA replication, the daughter strand that is synthesized continuously.
lectin Carbohydrate-binding proteins on a cell, not an antibody.
lepromin test A skin test to determine the presence of antibodies to *Mycobacterium leprae,* the cause of leprosy.
leukocidins Substances produced by some bacteria that can destroy neutrophils and macrophages.
leukocyte A white blood cell.
leukotriene A substance produced by mast cells and basophils that causes increased permeability of blood vessels and helps phagocytes attach to pathogens.
L form Prokaryotic cells that lack a cell wall; can return to walled state.
lichen A mutualistic relationship between a fungus and an alga or a cyanobacterium.
ligand *See* adhesin.
light-dependent (light) reaction The process by which light energy is used to convert ADP and phosphate to ATP. *See also* photophosphorylation.
light-independent (dark) reactions The process by which electrons and energy from ATP are used to reduce CO_2 to sugar. *See also* Calvin-Benson cycle.
light-repair enzyme *See* photolyase.
limnetic zone The surface zone of an inland body of water away from the shore.
Limulus amebocyte lysate (LAL) assay A test to detect the presence of bacterial endotoxins.
lipase An enzyme that breaks down triglycerides into their component glycerol and fatty acids.
lipid A non–water-soluble organic molecule, including triglycerides, phospholipids, and sterols.
lipid A A component of the gram-negative outer membrane; endotoxin.
lipid inclusion *See* inclusion.
lipopolysaccharide (LPS) A molecule consisting of a lipid and a polysaccharide, forming the outer membrane of gram-negative cell walls.
L-isomer Arrangement of four different atoms or groups around a carbon atom. *See* D-isomer.
lithotroph *See* autotroph.
littoral zone The region along the shore of the ocean or a large lake where there is considerable vegetation and where light penetrates to the bottom.
local infection An infection in which pathogens are limited to a small area of the body.
localized anaphylaxis An immediate hypersensitivity reaction that is restricted to a limited area of skin or mucous membrane; for example, hayfever, a skin rash, or asthma. *See also* systemic anaphylaxis.
logarithmic decline phase *See* death phase.
log phase The period of bacterial growth or logarithmic increase in cell numbers; also called exponential growth phase.
lophotrichous Having two or more flagella at one end of a cell.
luciferase An enzyme that accepts electrons from flavoproteins and emits a photon of light in bioluminescence.
lymphangitis Inflammation of lymph vessels.
lymphocyte A leukocyte involved in specific immune responses.
lyophilization Freezing a substance and sublimating the ice in a vacuum; also called freeze-drying.
lysis (1) Destruction of a cell by the rupture of the plasma membrane, resulting in a loss of cytoplasm. (2) In disease, a gradual period of decline.
lysogenic conversion The acquisition of new properties by a host cell infected by a lysogenic phage.
lysogenic cycle Stages in viral development that result in the incorporation of viral DNA into host DNA.
lysogeny A state in which phage DNA is incorporated into the host cell without lysis.
lysosome An organelle containing digestive enzymes.
lysozyme An enzyme capable of hydrolyzing bacterial cell walls.
lytic cycle A mechanism of phage multiplication that results in host cell lysis.

macrolide An antibiotic that inhibits protein synthesis; for example, erythromycin.
macromolecule A large organic molecule.
macrophage A phagocytic cell; a mature monocyte. *See* fixed macrophage, free wandering macrophage.
macule A flat, reddened skin lesion.
maculopapular A rash with macules and papules.
magnetosome An iron oxide inclusion, produced by some gram-negative bacteria, that acts like a magnet.
major histocompatibility complex (MHC) The genes that code for histocompatibility antigens; also known as human leukocyte antigen (HLA) complex.
malolactic fermentation The conversion of malic acid to lactic acid by lactic acid bacteria.
malt Germinated barley grains containing maltose, glucose, and amylase.
malting The germination of starchy grains resulting in glucose and maltose production.
margination The process by which phagocytes stick to the lining of blood vessels.
mast cell A type of cell found throughout the body that contains histamine and other substances that stimulate vasodilation.
matrix Fluid in mitochondria.
maximum growth temperature The highest temperature at which a species can grow.
M (microfold) cell Cells that take up and transfer antigens to lymphocytes, on Peyer's patches.
mechanical transmission The process by which arthropods transmit infections by carrying pathogens on their feet and other body parts.
medulla A lichen body consisting of algae (or cyanobacteria) and fungi.
meiosis A eukaryotic cell replication process that results in cells with half the chromosome number of the original cell.
membrane attack complex (MAC) Complement proteins C5–C9, which together make lesions in cell membranes that lead to cell death.
membrane filter A screenlike material with pores small enough to retain microorganisms; a 0.45-μm filter retains most bacteria.
memory cell A long-lived B or T cell responsible for the memory, or secondary, response.
memory response A rapid rise in antibody titer following exposure to an antigen after the primary response to that antigen; also called anamestic response or secondary response.
meningitis Inflammation of the meninges, the three membranes covering the brain and spinal cord.
merozoite A trophozoite of *Plasmodium* found in red blood cells or liver cells.
mesophile An organism that grows between about 10°C and 50°C; a moderate-temperature–loving microbe.
mesosome An irregular fold in the plasma membrane of a prokaryotic cell that is an artifact of preparation for microscopy.
messenger RNA (mRNA) The type of RNA molecule that directs the incorporation of amino acids into proteins.
metabolic pathway A sequence of enzymatically catalyzed reactions occurring in a cell.
metabolism The sum of all the chemical reactions that occur in a living cell.
metabolomics The study of small molecules in and around growing cells.
metacercaria The encysted stage of a fluke in its final intermediate host.
metachromatic granule A granule that stores inorganic phosphate and stains red with certain blue dyes; characteristic of *Corynebacterium diphtheriae*. Collectively known as volutin.
metagenomics The study of the genomes of uncultured organisms by the collection and sequencing of DNA from environmental samples.
methane The hydrocarbon CH_4, a flammable gas formed by the microbial decomposition of organic matter; natural gas.
methylase An enzyme that attaches methyl groups ($—CH_3$) to a molecule; methylated cytosine is protected from digestion by restriction enzymes.
microaerophile An organism that grows best in an environment with less molecular oxygen (O_2) than is normally found in air.

microarray DNA probes attached to a glass surface, used to identify nucleotide sequences in a sample of DNA.
micrometer (μm) A unit of measurement equal to 10^{-6}m.
microorganism A living organism too small to be seen with the naked eye; includes bacteria, fungi, protozoa, and microscopic algae; also includes viruses.
microRNA (miRNA) Small, single-stranded RNA that prevent translation of a complementary mRNA.
microtubule A hollow tube made of the protein tubulin; the structural unit of eukaryotic flagella and centrioles.
microwave Electromagnetic radiation with wavelength between 10^{21} and 10^{-3} m.
minimal bactericidal concentration (MBC) The lowest concentration of chemotherapeutic agent that will kill test microorganisms.
minimal inhibitory concentration (MIC) The lowest concentration of a chemotherapeutic agent that will prevent growth of the test microorganisms.
minimum growth temperature The lowest temperature at which a species will grow.
miracidium The free-swimming, ciliated larva of a fluke that hatches from the egg.
missense mutation A mutation that results in the substitution of an amino acid in a protein.
mitochondrion (plural: **mitochondria**) An organelle containing Krebs cycle enzymes and the electron transport chain.
mitosis A eukaryotic cell replication process in which the chromosomes are duplicated; usually followed by division of the cytoplasm of the cell.
mitosome Eukaryotic organelle derived form degenrate mitochondria, found in *Trichomonas* and *Giardia*.
MMWR *Morbidity and Mortality Weekly Report;* a CDC publication containing data on notifiable diseases and topics of special interest.
mole An amount of a chemical equal to the atomic weights of all the atoms in a molecule of the chemical.
molecular biology The science dealing with DNA and protein synthesis of living organisms.
molecular clock An evolution timeline based on nucleotide sequences in organisms.
molecular weight The sum of the atomic weights of all atoms making up a molecule.
molecule A combination of atoms forming a specific chemical compound.
monoclonal antibody (Mab) A specific antibody produced in vitro by a clone of B cells hybridized with cancerous cells.
monocyte A leukocyte that is the precursor of a macrophage.
monoecious Having both male and female reproductive capacities.
monomer A small molecule that collectively combines to form polymers.
monomorphic Having a single shape; most bacteria always present with a genetically determined shape. *See also* pleomorphic.
mononuclear phagocytic system A system of fixed macrophages located in the spleen, liver, lymph nodes, and red bone marrow.
monosaccharide A simple sugar consisting of 3–7 carbon atoms.
monotrichous Having a single flagellum.
morbidity (1) The incidence of a specific disease. (2) The condition of being diseased.
morbidity rate The number of people affected by a disease in a given period of time in relation to the total population.
mordant A substance added to a staining solution to make it stain more intensely.
mortality The number of deaths from a specific notifiable disease.
mortality rate The number of deaths resulting from a disease in a given period of time in relation to the total population.
most probable number (MPN) method A statistical determination of the number of coliforms per 100 ml of water or 100 g of food.
motility The ability of an organism to move by itself.
M protein A heat- and acid-resistant protein of streptococcal cell walls and fibrils.
mucous membranes Membranes that line body openings, including the intestinal tract, open to the exterior; also called mucosa.
mutagen An agent in the environment that brings about mutations.
mutation Any change in the nitrogenous base sequence of DNA.
mutation rate The probability that a gene will mutate each time a cell divides.
mutualism A type of symbiosis in which both organisms or populations are benefited.
mycelium A mass of long filaments of cells that branch and intertwine, typically found in molds.
mycolic acid Long-chained, branched fatty acids characteristic of members of the genus *Mycobacterium*.
mycology The scientific study of fungi.
mycorrhiza A fungus growing in symbiosis with plant roots.
mycosis A fungal infection.
mycotoxin A toxin produced by a fungus.

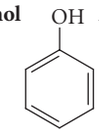
NAD^+ A coenzyme that functions in the removal and transfer of hydrogen ion (H^-) and electrons from substrate molecules.
$NADP^+$ A coenzyme similar to NAD^+.
nanobacteria Hypothesized bacteria well below the generally accepted lower limit diameter (about 200 nm) for bacteria.
nanometer (nm) A unit of measurement equal to 10^{-9} m, 10^{-3} μm.
nanotechnology Making molecular- or atomic-sized products.
NA (neuraminidase) spikes Antigenic projections from the outer lipid bilayer of *Influenzavirus*.
natural killer (NK) cell A lymphoid cell that destroys tumor cells and virus-infected cells.
naturally acquired active immunity Antibody production in response to an infectious disease.
naturally acquired passive immunity The natural transfer of humoral antibodies, for example, transplacental transfer.
natural selection Process by which organisms with certain inherited characteristics are more likely to survive and reproduce than organisms with other characteristics.
necrosis Tissue death.
negative (indirect) selection The process of identifying mutations by selecting cells that do not grow using replica plating.
negative staining A procedure that results in colorless bacteria against a stained background.
neurotoxin An exotoxin that interferes with normal nerve impulse conduction.
neutralization An antigen–antibody reaction that inactivates a bacterial exotoxin or virus.
neutron An uncharged particle in the nucleus of an atom.
neutrophil A highly phagocytic granulocyte; also called polymorphonuclear leukocyte (PMN) or polymorph.
nitrification The oxidation of nitrogen in ammonia to produce nitrate.
nitrogen cycle The series of processes that converts nitrogen (N_2) to organic substances and back to nitrogen in nature.
nitrogen fixation The conversion of nitrogen (N_2) into ammonia.
nitrosamine A carcinogen formed by the combination of nitrite and amino acids.
noncommunicable disease A disease that is not transmitted from one person to another.
noncompetitive inhibitor An inhibitory chemical that does not compete with the substrate for an enzyme's active site. *See also* allosteric inhibition; competitive inhibitor.
noncyclic photophosphorylation The movement of an electron from chlorophyll to NAD^+; plant and cyanobacterial photophosphorylation.
nonionizing radiation Short-wavelength radiation that does not cause ionization; ultraviolet (UV) radiation is an example.
non-nucleoside inhibitor A drug that binds with and inhibits the action of the HIV reverse transcriptase enzyme.
nonsense codon A codon that does not encode any amino acid.
nonsense mutation A base substitution in DNA that results in a nonsense codon.
normal microbiota The microorganisms that colonize a host without causing disease; also called normal flora.
nosocomial infection *See* healthcare-associated infection.
notifiable infectious disease A disease that physicians must report to the U.S. Public Health Service; also called reportable disease.

nuclear envelope The double membrane that separates the nucleus from the cytoplasm in a eukaryotic cell.
nuclear pore An opening in the nuclear envelope through which materials enter and exit the nucleus.
nucleic acid A macromolecule consisting of nucleotides; DNA and RNA are nucleic acids.
nucleic acid amplification test (NAAT) Test to identify an organism without culturing by making copies (amplifying) nucleic acid sequences that are specific for the organism being detected.
nucleic acid hybridization The process of combining single complementary strands of DNA.
nucleic acid vaccine A vaccine made up of DNA, usually in the form of a plasmid.
nucleoid The region in a bacterial cell containing the chromosome.
nucleolus (plural: nucleoli) An area in a eukaryotic nucleus where rRNA is synthesized.
nucleoside A compound consisting of a purine or pyrimidine base and a pentose sugar.
nucleoside reverse transcriptase inhibitor A nucleoside analog antiretroviral drug.
nucleotide A compound consisting of a purine or pyrimidine base, a five-carbon sugar, and a phosphate.
nucleotide (or nucleoside) analog A chemical that is structurally similar to the normal nucleotide or nucleoside in nucleic acids but with altered base-pairing properties.
nucleotide excision repair The repair of DNA involving removal of defective nucleotides and replacement with functional ones.
nucleus (1) The part of an atom consisting of the protons and neutrons. (2) The part of a eukaryotic cell that contains the genetic material.
numerical identification Bacterial identification schemes in which test values are assigned a number.
nutrient agar Nutrient broth containing agar.
nutrient broth A complex medium made of beef extract and peptone.

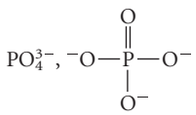
O antigen Polysaccharide antigens in the outer membrane of gram-negative bacteria, identified by serological testing.
objective lenses In a compound light microscope, the lenses closest to the specimen.
obligate aerobe An organism that requires molecular oxygen (O_2) to live.
obligate anaerobe An organism that does not use molecular oxygen (O_2) and is killed in the presence of O_2.
obligate halophile An organism that requires high osmotic pressures such as high concentrations of NaCl.
ocular lens In a compound light microscope, the lens closest to the viewer; also called the eyepiece.
oligodynamic action The ability of small amounts of a heavy metal compound to exert antimicrobial activity.
oligosaccharide A carbohydrate consisting of 2 to approximately 20 monosaccharides.
oncogene A gene that can bring about malignant transformation.
oncogenic virus A virus that is capable of producing tumors; also called oncovirus.
oocyst An encysted apicomplexan zygote in which cell division occurs to form the next infectious stage.
Opa A bacterial outer membrane protein; cells with Opa form opaque colonies.
operator The region of DNA adjacent to structural genes that controls their transcription.
operon The operator and promoter sites and structural genes they control.
opportunistic pathogen A microorganism that does not ordinarily cause a disease but can become pathogenic under certain circumstances.
opsonization The enhancement of phagocytosis by coating microorganisms with certain serum proteins (opsonins); also called immune adherence.
optimum growth temperature The temperature at which a species grows best.
order A taxonomic classification between class and family.
organotroph *See* heterotroph.
organelle A membrane-enclosed structure within eukaryotic cells.
organic compound A molecule that contains carbon and hydrogen.
organic growth factor An essential organic compound that an organism is unable to synthesize.
osmosis The net movement of solvent molecules across a selectively permeable membrane from an area of lower solute concentration to an area of higher solute concentration.
osmotic lysis Rupture of the plasma membrane resulting from movement of water into the cell.
osmotic pressure The force with which a solvent moves from a solution of lower solute concentration to a solution of higher solute concentration.
oxidation The removal of electrons from a molecule.
oxidation pond A method of secondary sewage treatment by microbial activity in a shallow standing pond of water.
oxidation-reduction A coupled reaction in which one substance is oxidized and one is reduced; also called redox reaction.
oxidative phosphorylation The synthesis of ATP coupled with electron transport.
oxygenic Producing oxygen, as in plant and cyanobacterial photosynthesis.
ozone O_3.

PAMP (pathogen-associated molecular patterns) Molecules present on pathogens and not self.
pandemic disease An epidemic that occurs worldwide.
papule Small, solid elevation of the skin.
parasite An organism that derives nutrients from a living host.
parasitism A symbiotic relationship in which one organism (the parasite) exploits another (the host) without providing any benefit in return.
parasitology The scientific study of parasitic protozoa and worms.
parenteral route A portal of entry for pathogens by deposition directly into tissues beneath the skin and mucous membranes.
pasteurization The process of mild heating to kill particular spoilage microorganisms or pathogens.
pathogen A disease-causing organism.
pathogenesis The manner in which a disease develops.
pathogenicity The ability of a microorganism to cause disease by overcoming the defenses of a host.
pathology The scientific study of disease.
pellicle (1) The flexible covering of some protozoa. (2) Scum on the surface of a liquid medium.
penicillins A group of antibiotics produced either by *Penicillium* (natural penicillins) or by adding side chains to the β-lactam ring (semisynthetic penicillins).
pentose phosphate pathway A metabolic pathway that can occur simultaneously with glycolysis to produce pentoses and NADH without ATP production; also called hexose monophosphate shunt.
peptide bond A bond joining the amino group of one amino acid to the carboxyl group of a second amino acid with the loss of a water molecule.
peptidoglycan The structural molecule of bacterial cell walls consisting of the molecules N-acetylglucosamine, N-acetylmuramic acid, tetrapeptide side chain, and peptide side chain.
perforin Protein that makes a pore in a target cell membrane, released by cytotoxic T lymphocytes.
pericarditis Inflammation of the pericardium, the sac around the heart.
period of convalescence The recovery period, when the body returns to its predisease state.
peripheral nervous system (PNS) The nerves that connect the outlying parts of the body with the central nervous system.
periplasm The region of a gram-negative cell wall between the outer membrane and the cytoplasmic membrane.
peritrichous Having flagella distributed over the entire cell.
peroxidase An enzyme that destroys hydrogen peroxide: $H_2O_2 + 2\,H^+\,2\,H_2O$
peroxide anion An oxygen anion consisting of two atoms of oxygen (O_2^{-2}).
peroxisome Organelle that oxidizes amino acids, fatty acids, and alcohol.
peroxygen A class of oxidizing-type sterilizing disinfectants.
persistent viral infection A disease process that occurs gradually over a long period.
Peyer's patches Lymphoid organs on the intestinal wall.

PFU (plaque-forming units) Visible clearing in a bacterial culture caused by lysis of bacterial cells by bacteriophages.
pH The symbol for hydrogen ion (H^1) concentration; a measure of the relative acidity or alkalinity of a solution.
phage *See* bacteriophage.
phage conversion Genetic change in the host cell resulting from infection by a bacteriophage.
phage typing A method of identifying bacteria using specific strains of bacteriophages.
phagocyte A cell capable of engulfing and digesting particles that are harmful to the body.
phagocytosis The ingestion of particles by eukaryotic cells.
phagolysosome A digestive vacuole.
phagosome A food vacuole of a phagocyte; also called a phagocytic vesicle.
phalloidin A peptide toxin produced by *Amanita phalloides,* affects plasma membrane function.
phase-contrast microscope A compound light microscope that allows examination of structures inside cells through the use of a special condenser.
phenol Also called carbolic acid.



phenolic A derivative of phenol used as a disinfectant.
phenotype The external manifestations of an organism's genotype, or genetic makeup.
phosphate group A portion of a phosphoric acid molecule attached to some other molecule, P,



phospholipid A complex lipid composed of glycerol, two fatty acids, and a phosphate group.
phosphorus cycle The various solubility stages of phosphorus in the environment.
phosphorylation The addition of a phosphate group to an organic molecule.
photoautotroph An organism that uses light as its energy source and carbon dioxide (CO_2) as its carbon source.
photoheterotroph An organism that uses light as its energy source and an organic carbon source.
photolyase An enzyme that splits thymine dimers in the presence of visible light.
photophosphorylation The production of ATP in a series of redox reactions; electrons from chlorophyll initiate the reactions.
photosynthesis The conversion of light energy from the sun into chemical energy; the light-fueled synthesis of carbohydrate from carbon dioxide (CO_2).
phototaxis Movement in response to the presence of light.
phototroph An organism that uses light at its primary energy source.
phylogeny The evolutionary history of a group of organisms; phylogenetic relationships are evolutionary relationships.
phylum A taxonomic classification between kingdom and class.
phytoplankton Free-floating photoautotrophs.
pilus (plural: pili) An appendage on a bacterial cell used for conjugation and gliding motility.
pinocytosis Taking in molecules by infolding of the plasma membrane, in eukaryotes.
plankton Free-floating aquatic organisms.
Plantae The kingdom composed of multicellular eukaryotes with cellulose cell walls.
plaque A clearing in a bacterial lawn resulting from lysis by phages. *See also* dental plaque.
plasma (1) The liquid portion of blood in which the formed elements are suspended. (2) Excited gases used for sterilizing.
plasma cell A cell that an activated B cell differentiates into; plasma cells manufacture specific antibodies.
plasma (cytoplasmic) membrane The selectively permeable membrane enclosing the cytoplasm of a cell; the outer layer in animal cells, internal to the cell wall in other organisms.
plasmid A small circular DNA molecule that replicates independently of the chromosome.
plasmodium (1) A multinucleated mass of protoplasm, as in plasmodial slime molds. (2) When written as a genus, refers to the causative agent of malaria.
plasmogamy Fusion of the cytoplasm of two cells; occurs in the sexual stage of a fungal life cycle.
plasmolysis Loss of water from a cell in a hypertonic environment.
plate count A method of determining the number of bacteria in a sample by counting the number of colony-forming units on a solid culture medium.
pleomorphic Having many shapes, characteristic of certain bacteria.
pluripotent A cell that can differentiate into a many different types of tissue cells.
pneumonia Inflammation of the lungs.
point mutation *See* base substitution.
polar flagella Having flagella at one or both ends of a cell.
polar molecule A molecule with an unequal distribution of charges.
polymer A molecule consisting of a sequence of similar molecules, or monomers.
polymerase chain reaction (PCR) A technique using DNA polymerase to make multiple copies of a DNA template in vitro. *See also* cDNA.
polymorphonuclear leukocyte (PMN) *See* neutrophil.
polypeptide (1) A chain of amino acids. (2) A group of antibiotics.
polysaccharide A carbohydrate consisting of 8 or more monosaccharides joined through dehydration synthesis.
porins A type of protein in the outer membrane of gram-negative cell walls that permits the passage of small molecules.
portal of entry The avenue by which a pathogen gains access to the body.
portal of exit The route by which a pathogen leaves the body.
positive (direct) selection A procedure for picking out mutant cells by growing them.
pour plate method A method of inoculating a solid nutrient medium by mixing bacteria in the melted medium and pouring the medium into a Petri dish to solidify.
prebiotics Chemicals that promote growth of beneficial bacteria in the body.
precipitation reaction A reaction between soluble antigens and multivalent antibodies to form visible aggregates.
precipitin ring test A precipitation test performed in a capillary tube.
predisposing factor Anything that makes the body more susceptible to a disease or alters the course of a disease.
prevalence The fraction of a population having a specific disease at a given time.
primary cell line Human tissue cells that grow for only a few generations in vitro.
primary infection An acute infection that causes the initial illness.
primary metabolite A product of an industrial cell population produced during the time of rapid logarithmic growth. *See also* secondary metabolite.
primary producer An autotrophic organism, either chemotroph or phototroph, that converts carbon dioxide into organic compounds.
primary response Antibody production in response to the first contact with an antigen. *See also* memory response.
primary sewage treatment The removal of solids from sewage by allowing them to settle out and be held temporarily in tanks or ponds.
prion An infectious agent consisting of a self-replicating protein, with no detectable nucleic acids.
privileged site (tissue) An area of the body (or a tissue) that does not elicit an immune response.
probiotics Microbes inoculated into a host to occupy a niche and prevent growth of pathogens.
prodromal period The time following the incubation period when the first symptoms of illness appear.
profundal zone The deeper water under the limnetic zone in an inland body of water.
proglottid A body segment of a tapeworm containing both male and female organs.

prokaryote A cell whose genetic material is not enclosed in a nuclear envelope.
prokaryotic species A population of cells that share certain rRNA sequences; in conventional biochemical testing, it is a population of cells with similar characteristics.
promoter The starting site on a DNA strand for transcription of RNA by RNA polymerase.
prophage Phage DNA inserted into the host cell's DNA.
prophylactic Anything used to prevent disease.
prostaglandin A hormonelike substance that is released by damaged cells, intensifies inflammation.
prostheca A stalk or bud protruding from a prokaryotic cell.
protease An enzyme that digests protein (proteolytic enzymes).
protein A large molecule containing carbon, hydrogen, oxygen, and nitrogen (and sulfur); some proteins have a helical structure and others are pleated sheets.
protein kinase An enzyme that activates another protein by adding a P from ATP.
proteobacteria Gram-negative, chemoheterotrophic bacteria that possess a signature rRNA sequence.
proteomics The science of determining all of the proteins expressed in a cell.
protist Term used for unicellular and simple multicellular eukaryotes; usually protozoa and algae.
proton A positively charged particle in the nucleus of an atom.
protoplast A gram-positive bacterium or plant cell treated to remove the cell wall.
protoplast fusion A method of joining two cells by first removing their cell walls; used in genetic engineering.
protozoan (plural: protozoa) Unicellular eukaryotic organisms; usually chemoheterotrophic.
provirus Viral DNA that is integrated into the host cell's DNA.
pseudohypha A short chain of fungal cells that results from the lack of separation of daughter cells after budding.
pseudopod An extension of a eukaryotic cell that aids in locomotion and feeding.
psychrophile An organism that grows best at about 15°C and does not grow above 20°C; a cold-loving microbe.
pscyhrotroph An organism that is capable of growth between about 0°C and 30°C.
purines The class of nucleic acid bases that includes adenine and guanine.
purple nonsulfur bacteria Alphaproteobacteria; strictly anaerobic and phototrophic; grow on yeast extract in dark; use reduced organic compounds as electron donors for CO_2 fixation.
purple sulfur bacteria Gammaproteobacteria; strictly anaerobic and phototrophic; use reduced sulfur compounds as electron donors for CO_2 fixation.
pus An accumulation of dead phagocytes, dead bacterial cells, and fluid.
pustule A small pus-filled elevation of skin.
pyocyanin A blue-green pigment produced by *Pseudomonas aeruginosa*.
pyrimidines The class of nucleic acid bases that includes uracil, thymine, and cytosine.
quaternary ammonium compound (quat) A cationic detergent with four organic groups attached to a central nitrogen atom; used as a disinfectant.
quorum sensing The ability of bacteria to communicate and coordinate behavior via signaling molecules.

R Used to represent nonfunctional groups of a molecule. *See also* resistance factor.
rapid diagnostic test (RDT) A test that allows diagnosis of a disease within a few minutes.
rapid identification methods Bacterial identification tools that perform several biochemical tests simultaneously.
rapid plasma reagin (RPR) test A serological test for syphilis.
r-determinant A group of genes for antibiotic resistance carried on R factors.
RecA Catalyzes joining of DNA strands, facilitates recombination of DNA.
receptor An attachment for a pathogen on a host cell.
receptor-mediated endocytosis A type of pinocytosis in which molecules bound to proteins on the plasma membrane are taken in by infolding of the membrane.
recipient cell A cell that receives DNA from a donor cell during genetic recombination.
recombinant DNA (rDNA) A DNA molecule produced by combining DNA from two different sources.
recombinant DNA (rDNA) technology Manufacturing and manipulating genetic material in vitro; also called genetic engineering.
recombinant vaccine A vaccine made by recombinant DNA techniques.
redia A trematode larval stage that reproduces asexually to produce cercariae.
redox reaction *See* oxidation-reduction.
red tide A bloom of planktonic dinoflagellates.
reducing medium A culture medium containing ingredients that will remove dissolved oxygen from the medium to allow the growth of anaerobes.
reduction The addition of electrons to a molecule.
refractive index The relative velocity with which light passes through a substance.
relative risk A comparison of the risk of disease in two groups.
rennin An enzyme that forms curds as part of any dairy fermentation product; originally from calves' stomachs, now produced by molds and bacteria.
replica plating A method of inoculating a number of solid minimal culture media from an original plate to produce the same pattern of colonies on each plate.
replication fork The point where DNA strands separate and new strands will be synthesized.
repression The process by which a repressor protein can stop the synthesis of a protein.
repressor A protein that binds to the operator site to prevent transcription.
reservoir of infection A continual source of infection.
resistance The ability to ward off diseases through innate and adaptive immunity.
resistance (R) factor A bacterial plasmid carrying genes that determine resistance to antibiotics.
resistance transfer factor (RTF) A group of genes for replication and conjugation on the R factor.
resolution The ability to distinguish fine detail with a magnifying instrument; also called resolving power.
respiration A series of redox reactions in a membrane that generates ATP; the final electron acceptor is usually an inorganic molecule.
restriction enzyme An enzyme that cuts double-stranded DNA at specific sites between nucleotides.
reticulate body The intracellular growing stage of chlamydiae.
reticuloendothelial system *See* mononuclear phagocytic system.
retort A device for commercially sterilizing canned food by using steam under pressure; operates on the same principle as an autoclave but is much larger.
reverse genetics Genetic analysis that begins with a piece of DNA and proceeds to find out what it does.
reverse transcriptase An RNA-dependent DNA polymerase; an enzyme that synthesizes a complementary DNA from an RNA template.
reversible reaction A chemical reaction in which the end-products can readily revert to the original molecules.
RFLP Restriction fragment length polymorphism; a fragment resulting from restriction-enzyme digestion of DNA.
Rh factor An antigen on red blood cells of rhesus monkeys and most humans; possession makes the cells Rh^1.
rhizine A rootlike hypha that anchors a fungus to a surface.
ribonucleic acid (RNA) The class of nucleic acids that comprises messenger RNA, ribosomal RNA, and transfer RNA.
ribose A five-carbon sugar that is part of ribonucleotide molecules and RNA.
ribosomal RNA (rRNA) The type of RNA molecule that forms ribosomes.
ribosomal RNA (rRNA) sequencing Determination of the order of nucleotide bases in rRNA.
ribosome The site of protein synthesis in a cell, composed of RNA and protein.

ribotyping Classification or identification of bacteria based on rRNA genes.
ribozyme An enzyme consisting of RNA that specifically acts on strands of RNA to remove introns and splice together the remaining exons.
ring stage A young *Plasmodium* trophozoite that looks like a ring in a red blood cell.
RNAi RNA interference; stops gene expression at transcription by using a short interfering RNA to make double-stranded RNA.
RNA-induced silencing complex (RISC) A complex consisting of a protein and siRNA or miRNA that binds complementary mRNA, preventing transcription of the mRNA.
RNA primer A short strand of RNA used to start synthesis of the lagging strand of DNA, and to start the polymerase chain reaction.
root nodule A tumorlike growth on the roots of certain plants containing symbiotic nitrogen-fixing bacteria.
rotating biological contactor A method of secondary sewage treatment in which large disks are rotated while partially submerged in a sewage tank exposing sewage to microorganisms and aerobic conditions.
rough ER Endoplasmic reticulum with ribosomes on its surface.
roundworm An animal belonging to the phylum Nematoda.

S (Svedberg unit) Notes the relative rate of sedimentation during ultra-high speed centrifugation.
salt A substance that dissolves in water to cations and anions, neither of which is H^+ or OH^-.
sanitization The removal of microbes from eating utensils and food preparation areas.
saprophyte An organism that obtains its nutrients from dead organic matter.
sarcina (plural: sarcinae) (1) A group of eight bacteria that remain in a packet after dividing. (2) When written as a genus, refers to gram-positive, anaerobic cocci.
saturation (1) The condition in which the active site on an enzyme is occupied by the substrate or product at all times. (2) In a fatty acid, having no double bonds.
saxitoxin A neurotoxin produced by some dinoflagellates.
scanned-probe microscopy Microscopic technique used to obtain images of molecular shapes, to characterize chemical properties, and to determine temperature variations within a specimen.
scanning acoustic microscope (SAM) A microscope that uses high-frequency ultrasound waves to penetrate surfaces.
scanning electron microscope (SEM) An electron microscope that provides three-dimensional views of the specimen magnified 1000–10,000×.
scanning tunneling microscopy *See* scanned-probe microscopy.
schizogony The process of multiple fission, in which one organism divides to produce many daughter cells.
scientific nomenclature *See* binomial nomenclature.
sclerotia The compact mass of hardened mycelia of the fungus *Claviceps purpurea* that fills infected rye flowers; produces the toxin ergot.
scolex The head of a tapeworm, containing suckers and possibly hooks.
secondary infection An infection caused by an opportunistic microbe after a primary infection has weakened the host's defenses.
secondary metabolite A product of an industrial cell population produced after the microorganism has largely completed its period of rapid growth and is in a stationary phase of the growth cycle. *See also* primary metabolite.
secondary response *See* memory response.
secondary sewage treatment Biological degradation of the organic matter in wastewater following primary treatment.
secretory vesicle A membrane-enclosed sac produced by the endoplasmic reticulum (ER); transports synthesized material into cytoplasm.
selective medium A culture medium designed to suppress the growth of unwanted microorganisms and encourage the growth of desired ones.
selective permeability The property of a plasma membrane to allow certain molecules and ions to move through the membrane while restricting others.
selective toxicity The property of some antimicrobial agents to be toxic for a microorganism and nontoxic for the host.
self Host tissue.
semiconservative replication The process of DNA replication in which each double-stranded DNA molecule contains one original strand and one new strand.
sense codon A codon that codes for an amino acid.
sense strand (1 strand) Viral RNA that can act as mRNA.
sensitivity Percentage of positive samples correctly detected by a diagnostic test.
sentinel animal An organism in which changes can be measured to assess the extent of environmental contamination and its implication for human health.
sepsis The presence of a toxin or pathogenic organism in blood and tissue.
septate hypha A hypha consisting of uninucleate cell-like units.
septicemia The proliferation of pathogens in the blood, accompanied by fever; sometimes causes organ damage.
septic shock A sudden drop in blood pressure induced by bacterial toxins.
septum A cross-wall in a fungal hypha.
serial dilution The process of diluting a sample several times.
seroconversion A change in a person's response to an antigen in a serological test.
serological testing Techniques for identifying a microorganism based on its reaction with antibodies.
serology The branch of immunology that studies blood serum and antigen–antibody reactions in vitro.
serotype *See* serovar.
serovar A variation within a species; also called serotype.
serum The liquid remaining after blood plasma is clotted; contains antibodies (immunoglobulins).
sexual dimorphism The distinctly different appearance of adult male and female organisms.
sexual spore A spore formed by sexual reproduction.
Shiga toxin An exotoxin produced by *Shigella dysenteriae* and enterohemorrhagic *E. coli*.
shock Any life-threatening loss of blood pressure. *See also* septic shock.
short tandem repeats (STRs) Repeating sequences of 2- to 5-nucleotides.
shotgun sequencing A technique for determining the nucleotide sequence in an organism's genome.
shuttle vector A plasmid that can exist in several different species; used in genetic engineering.
siderophore Bacterial iron-binding proteins.
sign A change due to a disease that a person can observe and measure.
simple stain A method of staining microorganisms with a single basic dye.
singlet oxygen Highly reactive molecular oxygen (O_2^-).
siRNA Small interfering RNA; An intermediate in the RNAi process in which the long double-stranded RNA has been cut up into short (~21 nucleotides) double-stranded RNA.
site-directed mutagenesis Techniques used to modify a gene in a specific location to produce the desired polypeptide.
slide agglutination test A method of identifying an antigen by combining it with a specific antibody on a slide.
slime layer A glycocalyx that is unorganized and loosely attached to the cell wall.
sludge Solid matter obtained from sewage.
smear A thin film of material containing microorganisms, spread over the surface of a slide.
smooth ER Endoplasmic reticulum without ribosomes.
SNP Single nucleotide polymorphism (pronounced "snip"). Single base-pair variations in the genomes of a population, found in at least 1% of the population.
snRNP Small nuclear ribonucleoprotein (pronounced "snurp"). Short RNA transcript plus protein that combines with pre-mRNA to remove introns and join exons together.
solute A substance dissolved in another substance.
solvent A dissolving medium.
Southern blotting A technique that uses DNA probes to detect the presence of specific DNA in restriction fragments separated by electrophoresis.
specialized transduction The process of transferring a piece of cell DNA adjacent to a prophage to another cell.
species The most specific level in the taxonomic hierarchy. *See also* bacterial species; eukaryotic species; viral species.
specific epithet The second or species name in a scientific binomial. *See also* species.
specificity Percentage of false positive results given by a diagnostic test.

spectrum of microbial activity The range of distinctly different types of microorganisms affected by an antimicrobial drug; a wide range is referred to as a broad spectrum of activity.
spheroplast A gram-negative bacterium treated to damage the cell wall, resulting in a spherical cell.
spicule One of two external structures on the male roundworm used to guide sperm.
spike A carbohydrate-protein complex that projects from the surface of certain viruses.
spiral *See* spirillum and spirochete.
spirillum (plural: spirilla) (1) A helical or corkscrew-shaped bacterium. (2) When written as a genus, refers to aerobic, helical bacteria with clumps of polar flagella.
spirochete A corkscrew-shaped bacterium with axial filaments.
spontaneous generation The idea that life could arise spontaneously from nonliving matter.
spontaneous mutation A mutation that occurs without a mutagen.
sporadic disease A disease that occurs occasionally in a population.
sporangiophore An aerial hypha supporting a sporangium.
sporangiospore An asexual fungal spore formed within a sporangium.
sporangium A sac containing one or more spores.
spore A reproductive structure formed by fungi and actinomycetes. *See also* endospore.
sporogenesis *See* sporulation.
sporozoite A trophozoite of *Plasmodium* found in mosquitoes, infective for humans.
sporulation The process of spore and endospore formation; also called sporogenesis.
spread plate method A plate count method in which inoculum is spread over the surface of a solid culture medium.
staining Colorizing a sample with a dye to view through a microscope or to visualize specific structures.
staphylococci (singular: staphylococcus) Cocci in a grapelike cluster or broad sheet.
stationary phase The period in a bacterial growth curve when the number of cells dividing equals the number dying.
stem cell An undifferentiated cell that gives rise to a variety of specialized cells.
stereoisomers Two molecules consisting of the same atoms, arranged in the same manner but differing in their relative positions; mirror images; also called D-isomer and L-isomer.
sterile Free of microorganisms.
sterilization The removal of all microorganisms, including endospores.
steroid A specific group of lipids, including cholesterol and hormones.
stipe A stemlike supporting structure of multicellular algae and basidiomycetes.
storage vesicle Organelles that form from the Golgi complex; contain proteins made in the rough ER and processed in the Golgi complex.
strain Genetically different cells within a clone. *See* serovar.
streak plate method A method of isolating a culture by spreading microorganisms over the surface of a solid culture medium.
streptobacilli (singular: streptobacillus) Rods that remain attached in chains after cell division.
streptococci (singular: streptococcus) (1) Cocci that remain attached in chains after cell division. (2) When written as a genus, refers to gram-positive, catalase-negative bacteria.
streptokinase A blood-clot dissolving enzyme, produced by beta-hemolytic streptococci.
streptolysin A hemolytic enzyme, produced by streptococci.
structural gene A gene that determines the amino acid sequence of a protein.
subacute disease A disease with symptoms that are intermediate between acute and chronic.
subclinical infection An infection that does not cause a noticeable illness; also called inapparent infection.
subcutaneous mycosis A fungal infection of tissue beneath the skin.
substrate Any compound with which an enzyme reacts.
substrate-level phosphorylation The synthesis of ATP by direct transfer of a high-energy phosphate group from an intermediate metabolic compound to ADP.
subunit vaccine A vaccine consisting of an antigenetic fragment.
sulfhydryl group —SH.
sulfur cycle The various oxidation and reduction stages of sulfur in the environment, mostly due to the action of microorganisms.
sulfur granule *See* inclusion.
superantigen An antigen that activates many different T cells, thereby eliciting a large immune response.
superbug Bacterium resistant to a large number of antibiotics.
superficial mycosis A fungal infection localized in surface epidermal cells and along hair shafts.
superinfection The growth of a pathogen that has developed resistance to an antimicrobial drug being used; the growth of an opportunistic pathogen.
superoxide dismutase (SOD) An enzyme that destroys superoxide:

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

superoxide radical A toxic anion (O_2^-) with an unpaired electron.
surface-active agent Any compound that decreases the tension between molecules lying on the surface of a liquid; also called surfactant.
susceptibility The lack of resistance to a disease.
symbiosis The living together of two different organisms or populations.
symptom A change in body function that is felt by a patient as a result of a disease.
syncytium A multinucleated giant cell resulting from certain viral infections.
syndrome A specific group of signs or symptoms that accompany a disease.
synergism The principle whereby the effectiveness of two drugs used simultaneously is greater than that of either drug used alone.
synthesis reaction A chemical reaction in which two or more atoms combine to form a new, larger molecule.
synthetic drug A chemotherapeutic agent that is prepared from chemicals in a laboratory.
systematics The science organizing groups of organisms into a hierarchy.
systemic anaphylaxis A hypersensitivity reaction causing vasodilation and resulting in shock; also called anaphylactic shock.
systemic (generalized) infection An infection throughout the body.
systemic mycosis A fungal infection in deep tissues.

tachyzoite A rapidly growing trophozoite form of a protozoan.
T antigen An antigen in the nucleus of a tumor cell.
tapeworm A flatworm belonging to the class Cestoda.
target cell An infected body cell to which defensive cells of the immune system bind.
taxa Subdivisions used to classify organisms, e.g., domain, kingdom, phylum.
taxis Movement in response to an environmental stimulus.
taxonomy The science of the classification of organisms.
T cell A type of lymphocyte, which develops from a stem cell processed in the thymus gland, that is responsible for cell-mediated immunity. *See also* CTL (cytotoxic T lymphocyte), T helper cells, T regulatory cells.
TCRs (T cell receptors) Molecules on T cells that recognize antigens.
T helper (T_H) cell A specialized T cell that often interacts with an antigen before B cells interact with the antigen.
T regulatory (T_{reg}) cells Lymphocytes that appear to suppress other T cells.
T-dependent antigen An antigen that will stimulate the formation of antibodies only with the assistance of T helper cells. *See also* T-independent antigen.
teichoic acid A polysaccharide found in gram-positive cell walls.
telomere Noncoding regions of DNA at the ends of eukaryotic chromosomes.
teleomorph The sexual stage in the life cycle of a fungus; also refers to a fungus that produces both sexual and asexual spores.
temperate phage A phage capable of lysogeny.
temperature abuse Improper food storage at a temperature that allows bacteria to grow.
terminator The site on a DNA strand at which transcription ends.
tertiary sewage treatment A method of waste treatment that follows conventional secondary sewage treatment; nonbiodegradable pollutants and mineral nutrients are removed, usually by chemical or physical means.
tetrad A group of four cocci.

thallus The entire vegetative structure or body of a fungus, lichen, or alga.
thermal death point (TDP) The temperature required to kill all the bacteria in a liquid culture in 10 minutes.
thermal death time (TDT) The length of time required to kill all bacteria in a liquid culture at a given temperature.
thermoduric Heat resistant.
thermophile An organism whose optimum growth temperature is between 50°C and 60°C; a heat loving microbe.
thermophilic anaerobic spoilage Spoilage of canned foods due to the growth of thermophilic bacteria.
thylakoid A chlorophyll-containing membrane in a chloroplast. A bacterial thylakoid is also known as a chromatophore.
thymus A mammalian organ responsible for maturation of the immune system.
thymic selection Elimination of T cells that don't recognize self antigens (major histocompatibility complex).
tincture A solution in aqueous alcohol.
T-independent antigen An antigen that will stimulate the formation of antibodies without the assistance of T helper cells. *See also* T-dependent antigen.
tinea Fungal infection of hair, skin, or nails.
Ti plasmid A tumor-inducing plasmid that can be incorporated into a host plant chromosome; found in *Agrobacterium.*
titer An estimate of the amount of antibodies or viruses in a solution; determined by serial dilution and expressed as the reciprocal of the dilution.
TLR (Toll-like rceptor) Transmembrane protein of immune cells that recognizes pathogens and activates an immune response directed against those pathogens.
topoisomerase Enzyme that relaxes supercoiling of DNA ahead of replication form; separates DNA circles at the end of DNA replication.
total magnification The magnification of a microscopic specimen, determined by multiplying the ocular lens magnification by the objective lens magnification.
toxemia The presence of toxins in the blood.
toxigenicity The capacity of a microorganism to produce a toxin.
toxin Any poisonous substance produced by a microorganism.
toxoid An inactivated toxin.
T plasmid An *Agrobacterium* plasmid carrying genes for tumor induction in plants.
trace element A chemical element required in small amounts for growth.
trans Hydrogen atoms on opposite side across a double bond in a fatty acid. *See* cis.
transamination The transfer of an amino group from an amino acid to another organic acid.
transcription The process of synthesizing RNA from a DNA template.
transduction The transfer of DNA from one cell to another by a bacteriophage. *See also* generalized transduction; specialized transduction.
transferrin One of several human iron-binding proteins that reduce iron available to a pathogen.
transfer RNA (tRNA) The type of RNA molecule that brings amino acids to the ribosomal site where they are incorporated into proteins.
transfer vesicle Membrane-bound sacs that move proteins from the Golgi complex to specific areas in the cell.
transformation (1) The process in which genes are transferred from one bacterium to another as "naked" DNA in solution. (2) The changing of a normal cell into a cancerous cell.
transient microbiota The microorganisms that are present in an animal for a short time without causing a disease.
translation The use of mRNA as a template in the synthesis of protein.
transmission electron microscope (TEM) An electron microscope that provides high magnifications (10,000–100,000×) of thin sections of a specimen.
transport media Media used to keep microorganisms alive between sample collection and laboratory testing; usually used for clinical samples.
transport vesicle Membrane-bound sacs that move proteins from the rough ER to the Golgi complex.
transporter protein A carrier protein in the plasma membrane.
transposon A small piece of DNA that can move from one DNA molecule to another.
trickling filter A method of secondary sewage treatment in which sewage is sprayed out of rotating arms onto a bed of rocks or similar materials, exposing the sewage to highly aerobic conditions and microorganisms.
triglyceride A simple lipid consisting of glycerol and three fatty acids.
triplex agent A short segment of DNA that binds to a target area on a double strand of DNA blocking transcription.
trophophase The period in the production curve of an industrial cell population in which the primary metabolites are formed; a period of rapid, logarithmic growth. *See also* idiophase.
trophozoite The vegetative form of a protozoan.
tuberculin skin test A skin test used to detect the presence of antibodies to *Mycobacterium tuberculosis.*
tumor necrosis factor (TNF) A polypeptide released by phagocytes in response to bacterial endotoxins.
tumor-specific transplantation antigen (TSTA) A viral antigen on the surface of a transformed cell.
turbidity The cloudiness of a suspension.
turnover number The number of substrate molecules acted on per enzyme molecule per second.
two-photon microscope A light microscope that uses fluorescent stains and long wavelength light.

ubiquinone A low–molecular weight, nonprotein carrier in an electron transport chain; also called coenzyme Q.
ultra-high-temperature (UHT) treatment A method of treating food with high temperatures (140–150°C) for very short times to make the food sterile so that it can be stored at room temperature.
uncoating The separation of viral nucleic acid from its protein coat.
undulating membrane A highly modified flagellum on some protozoa.
unsaturated A fatty acid with one or more double bonds.
use-dilution test A method of determining the effectiveness of a disinfectant using serial dilutions.

vaccination The process of conferring immunity by administering a vaccine; also called immunization.
vaccine A preparation of killed, inactivated, or attenuated microorganisms or toxoids to induce artificially acquired active immunity.
vacuole An intracellular inclusion, in eukaryotic cells, surrounded by a plasma membrane; in prokaryotic cells, surrounded by a proteinaceous membrane.
valence The combining capacity of an atom or a molecule.
vancomycin An antibiotic that inhibits cell wall synthesis.
variolation An early method of vaccination using infected material from a patient.
vasodilation Dilation or enlargement of blood vessels.
VDRL test A rapid screening test to detect the presence of antibodies against *Treponema pallidum*. (VDRL stands for Venereal Disease Research Laboratory.)
vector (1) A plasmid or virus used in genetic engineering to insert genes into a cell. (2) An arthropod that carries disease-causing organisms from one host to another.
vegetative Referring to cells involved with obtaining nutrients, as opposed to reproduction.
vehicle transmission The transmission of a pathogen by an inanimate reservoir.
vertical gene transfer Transfer of genes from an organism or cell to its offspring.
vesicle (1) A small serum-filled elevation of the skin. (2) Smooth oval bodies formed in plant roots by mycorrhizae.
V factor NAD^+ or $NADP^+$.
vibrio (1) A curved or comma-shaped bacterium. (2) When written as a genus (*Vibrio*), a gram-negative, motile, facultatively anaerobic curved rod.
viral hemagglutination The ability of certain viruses to cause the clumping of red blood cells in vitro.
viral hemagglutination inhibition test A neutralization test in which antibodies against particular viruses prevent the viruses from clumping red blood cells in vitro.

viral species A group of viruses sharing the same genetic information and ecological niche.
viremia The presence of viruses in the blood.
virion A complete, fully developed viral particle.
viroid Infectious RNA.
virology The scientific study of viruses.
virulence The degree of pathogenicity of a microorganism.
virus A submicroscopic, parasitic, filterable agent consisting of a nucleic acid surrounded by a protein coat.
volutin Stored inorganic phosphate in a prokaryotic cell. *See also* metachromatic granule.

Western blotting A technique that uses antibodies to detect the presence of specific proteins separated by electrophoresis.
whey The fluid portion of milk that separates from curd.

xenobiotics Synthetic chemicals that are not readily degraded by microorganisms.
xenodiagnosis A method of diagnosis based on exposing a parasite-free normal host to the parasite and then examining the host for parasites.
xenotransplantation product A tissue graft from another species; also called xenograft.
X factor Substances from the heme fraction of blood hemoglobin.

yeast Nonfilamentous, unicellular fungi.
yeast infection Disease caused by growth of certain yeasts in a susceptible host.

zone of inhibition The area of no bacterial growth around an antimicrobial agent in the disk-diffusion method.
zoonosis A disease that occurs primarily in wild and domestic animals but can be transmitted to humans.
zoospore An asexual algal spore; has two flagella.
zygospore A sexual fungal spore characteristic of the zygomycetes.
zygote A diploid cell produced by the fusion of two haploid gametes.

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Chapter 25. Opener: David M. Phillips/Science Source. **ITC**: JGI/Blend Images/Corbis. **25.3:** Hutton D. Slade, Microbiology Review, 44:331–384, 1980, F5, ASM News. **25.10:** London School of Hygiene & Tropical Medicine/Photo Researchers. **25.11:** I. Rosenshine et al., "A Pathogenic Bacterium Triggers Epithelial Signals to Form a Functional Bacterial Receptor That Mediates Actin Pseudopod Formation," *The EMB0 Journal,* 1996 June 3; 15(11):2613–24, cover. **25.12:** SPL/Science Source. **25.13:** P. Marazzi/Science Source. **25.14:** Linda Stannard, U. of Cape Town/Science Source. **25.15:** James Cavallini/Science Source. **25.16:** From Robert Owen et al. "Ultrastructural Observations of Giardiasis in a Murin Model," *Gastroenterology* 76:757–769. © 1979 by the American Gastroenterological Assoc. **25.17:** EM Unit, London School of Hygiene & Tropical Medicine, London, UK. **25.18:** Armed Forces Institute of Pathology. **25.20:** Original photo by A. Kimball from A Pictorial Presentation of Parasites edited by Herman Zaiman. **25.21:** Armed Forces Institute of Pathology. **25.22:** Cath Ellis/Science Source. **25.23:** Sinclair Stammers/ Science Source. **25.24:** Mae Melvin, CDC. **25.25.1:** KariDesign/Shutterstock. **25.25.2:** Eric Isselée/Shutterstock. **25.25.3:** Dickson Despommier, Mailman School of Public Health, Columbia University (www.trichinella.org). **25.25.4:** Dickson Despommier, Mailman School of Public Health, Columbia University (www.trichinella.org). **AM:** The LIFE Picture Collection/Getty Images. **BP.2:** Yuan Man/Xinhua/Photoshot/Newscom. **BP.3:** Ami Images/Science Source. **BP.4:** Sean Sprague/Alamy. **CF:** CDC. **DIF 25.1:** Laura Ahonen. **DIF 25.2:** Mauro Rodrigues/Shutterstock. **DIF 25.3.1:** Southern Illinois U./Science Source. **DIF 25.3.2:** Custom Medical Stock Photo. **DIF 25.4:** E. L. Palmer, CDC. **DIF 25.5:** Melanie Moser, CDC/DPDx.

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Note: a *t* following a page number indicates tabular material, an *f* following a page number indicates a figure or illustration, a *b* indicates a boxed feature, a *c* indicates a Clinical Case, and a page number in **boldface** indicates a definition.

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