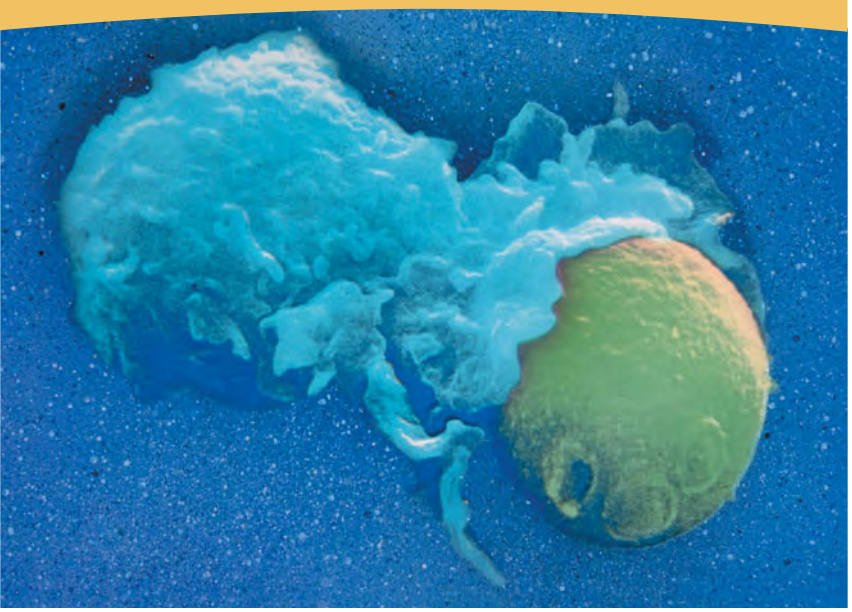
43

The Immune System



▲ **Figure 43.1 How do an animal's immune cells recognize foreign cells?**

KEY CONCEPTS

OVERVIEW

Recognition and Response

Pathogens, agents that cause disease, infect a wide range of animals. For a virus, bacterium, fungus, or other pathogen, the internal environment of an animal is a nearly ideal habitat. The animal body offers a ready source of nutrients, a protected setting for growth and reproduction, and a means of transport to new environments. From the perspective of a cold or flu virus, we are wonderful hosts. From our vantage point, things are not so ideal. Fortunately, adaptations have arisen over the course of evolution that protect animals against many invaders.

Dedicated immune cells in the body fluids and tissues of most animals specifically interact with and destroy pathogens. As shown in **Figure 43.1** (a colorized scanning electron micrograph), an immune cell called a macrophage (blue) can engulf a yeast cell (green). Additional responses to infection take many forms, including proteins that punch holes in bacterial membranes or block viruses from entering body cells. These and other defenses make up the **immune system**, which enables an animal to avoid or limit many infections. A foreign molecule or cell doesn't have to be pathogenic to elicit an immune response, but we'll focus here on the immune system's role in defending against pathogens.

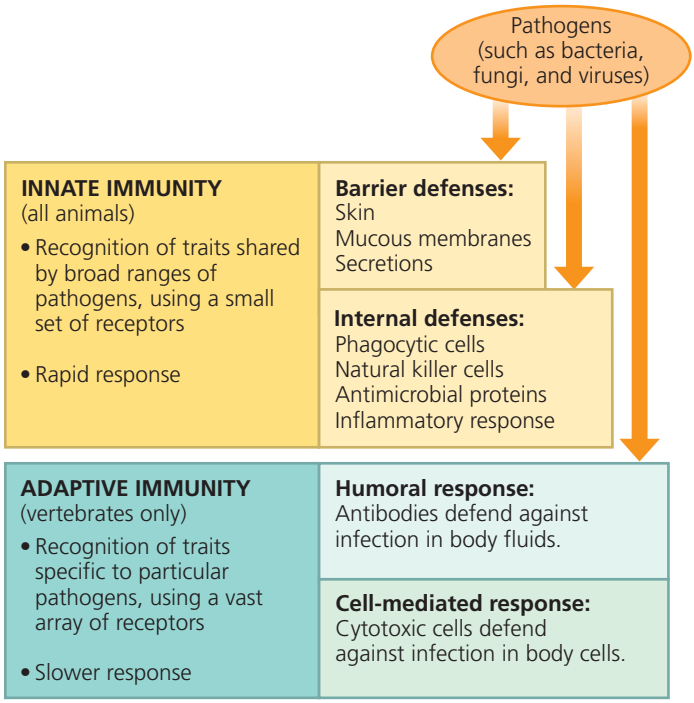
All animals have **innate immunity**, a defense that is active immediately upon infection and is the same whether or not the pathogen has been encountered previously. Innate immunity includes an outer covering, such as a skin or shell, that provides a significant barrier to entry by microbes. Sealing off the entire body surface is impossible, however, because gas exchange, nutrition, and reproduction require openings to the environment. Chemical secretions that trap or kill microbes guard the body's entrances and exits, while the linings of the digestive tract, airway, and other exchange surfaces provide additional barriers to infection.

If a pathogen breaches barrier defenses and enters the body, the problem of how to fend off attack changes substantially. Housed within the body fluids and tissues, the invader is no longer an outsider. To fight infections, an animal's immune system must detect foreign particles and cells within the body. In other words, a properly functioning immune system distinguishes nonself from self. Detection of nonself is accomplished by *molecular recognition*, in which receptor molecules bind specifically to molecules from foreign cells or viruses.

In innate immunity, a small preset group of receptor proteins bind to molecules or structures that are absent from animal bodies but common to a group of viruses, bacteria, or other microbes. Binding of an innate immune receptor to a foreign molecule activates internal defenses, enabling responses to a very broad range of pathogens.

A different type of molecular recognition provides the basis for **adaptive immunity**, a defense found only in vertebrates. Animals with adaptive immunity produce a vast arsenal of receptors, each of which recognizes a feature typically found only on a particular part of a particular molecule in a particular pathogen. As a result, recognition and response in adaptive immunity occur with tremendous specificity.

The adaptive immune response, also known as the acquired immune response, is activated after the innate immune response and develops more slowly. The names *adaptive* and



▲ **Figure 43.2 Overview of animal immunity.** Immune responses in animals can be divided into innate and adaptive immunity. Some components of innate immunity contribute to activation of adaptive immune defenses.

acquired reflect the fact that this immune response is enhanced by previous exposure to the infecting pathogen. Examples of adaptive responses include the synthesis of proteins that inactivate a bacterial toxin and the targeted killing of a virus-infected body cell.

Figure 43.2 provides an overview of the basic components of innate and adaptive immunity. In this chapter, you will learn how each type of immunity protects animals from disease. You will also examine how pathogens can avoid or overwhelm the immune system and how defects in the immune system can imperil an animal's health.

CONCEPT **43.1**

In innate immunity, recognition and response rely on traits common to groups of pathogens

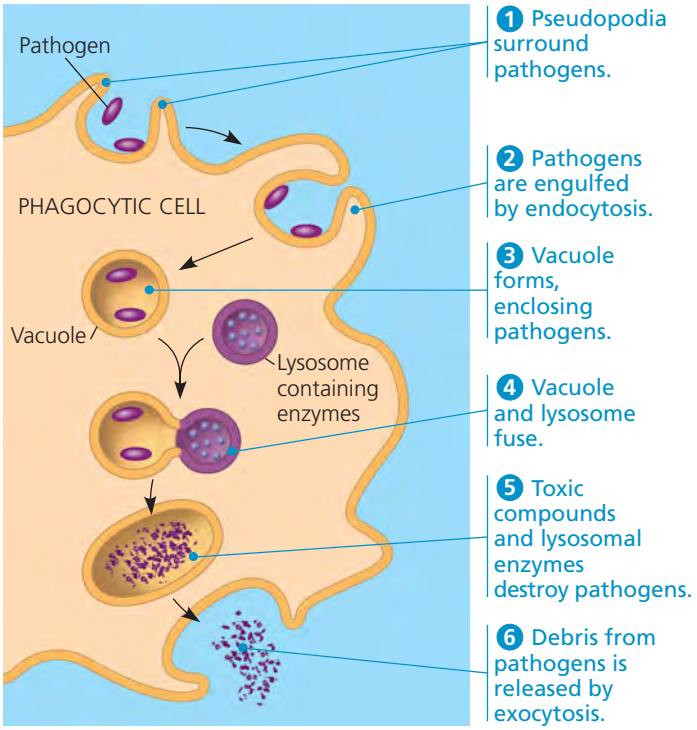
Innate immunity is found in all animals (as well as in plants). In exploring innate immunity, we'll begin with invertebrates, which repel and fight infection with only this type of immunity. We'll then turn to vertebrates, in which innate immunity serves both as an immediate defense against infection and as the foundation for adaptive immune defenses.

Innate Immunity of Invertebrates

The great success of insects in terrestrial and freshwater habitats teeming with diverse microbes highlights the effectiveness of invertebrate innate immunity. In each of these environments, insects rely on their exoskeleton as a first line of defense against infection. Composed largely of the polysaccharide chitin, the exoskeleton provides an effective barrier defense against most pathogens. A chitin-based barrier is also present in the insect intestine, where it blocks infection by many pathogens ingested with food. **Lysozyme**, an enzyme that breaks down bacterial cell walls, further protects the insect digestive system.

Any pathogen that breaches an insect's barrier defenses encounters a number of internal immune defenses. Immune cells called *hemocytes* travel throughout the body in the hemolymph, the insect circulatory fluid. Some hemocytes carry out a defense called **phagocytosis**, the cellular ingestion and digestion of bacteria and other foreign substances **(Figure 43.3)**. Other hemocytes trigger the production of chemicals that kill pathogens and help entrap large parasites, such as *Plasmodium*, the parasite of mosquitoes that causes malaria. In addition, encounters with pathogens in the hemolymph cause hemocytes and certain other cells to secrete *antimicrobial peptides*, which are short chains of amino acids. The antimicrobial peptides circulate throughout the body of the insect **(Figure 43.4)** and inactivate or kill fungi and bacteria by disrupting their plasma membranes.

Immune cells of insects bind to molecules found only in the outer layers of fungi or bacteria. Fungal cell walls contain certain unique polysaccharides, whereas bacterial cell walls have polymers containing combinations of sugars and amino



▲ **Figure 43.3 Phagocytosis.** This schematic depicts events in the ingestion and destruction of a microbe by a typical phagocytic cell.

▲ **Figure 43.4 An inducible innate immune response.** These fruit flies were engineered to express the green fluorescent protein (GFP) gene upon activation of the innate immune response. The fly on the top was injected with bacteria; the fly on the bottom was not. Only the infected fly activates antimicrobial peptide genes, produces GFP, and glows a bright green under fluorescent light.

acids not found in animal cells. Such macromolecules serve as identity tags in the process of pathogen recognition. Insect immune cells secrete specialized recognition proteins, each of which binds to a macromolecule characteristic of fungi or a broad class of bacteria.

Innate immune responses are distinct for different classes of pathogens. For example, when the fungus *Neurospora crassa* infects a fruit fly, pieces of the fungal cell wall bind a recognition protein. Together, the complex activates the protein Toll, a receptor on the surface of hemocytes. Signal transduction from the Toll receptor to the cell nucleus leads to synthesis of a set of antimicrobial peptides active against fungi. If the fly is instead infected by the bacterium *Micrococcus luteus*, a different recognition protein is activated, and the fly produces a different set of antimicrobial peptides effective against *M. luteus* and many related bacteria.

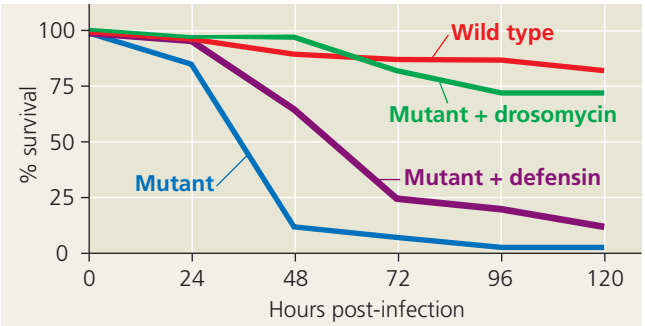
Because fruit flies secrete many distinct antimicrobial peptides in response to a single infection, it is difficult to study the activity of any one peptide. To get around this problem, Bruno Lemaitre and fellow researchers used modern genetic techniques to reprogram the fly immune system **(Figure 43.5)**. They found that the synthesis of a single type of antimicrobial peptide in the fly's body could provide an effective immune defense. They also showed that particular antimicrobial peptides act against different kinds of pathogens.

▼ **Figure 43.5** **INQUIRY**

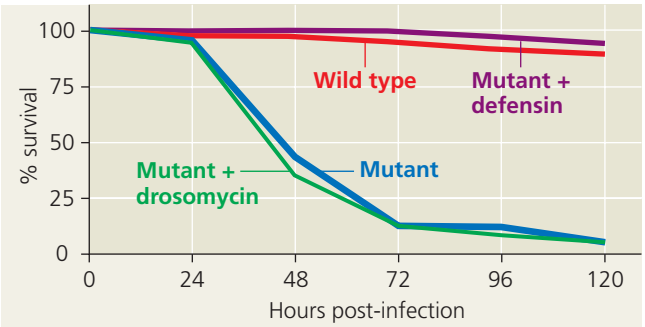
Can a single antimicrobial peptide protect fruit flies against infection?

EXPERIMENT In 2002, Bruno Lemaitre and colleagues in France devised a novel strategy to test the function of a single antimicrobial peptide. They began with a mutant fruit fly strain in which pathogens are recognized but the signaling that would normally trigger innate immune responses is blocked. As a result, the mutant flies do not make any antimicrobial peptides. The researchers then genetically engineered some of the mutant fruit flies to express significant amounts of a single antimicrobial peptide, either drosomycin or defensin. The scientists infected the various flies with the fungus *Neurospora crassa* and monitored survival over a five-day period. They repeated the procedure for infection by the bacterium *Micrococcus luteus*.

RESULTS



Fruit fly survival after infection by *N. crassa* fungi



Fruit fly survival after infection by *M. luteus* bacteria

CONCLUSION Each of the two antimicrobial peptides provided a protective immune response. Furthermore, the different peptides defended against different pathogens. Drosomycin was effective against *N. crassa*, and defensin was effective against *M. luteus*.

SOURCE P. Tzou, J. Reichhart, and B. Lemaitre, Constitutive expression of a single antimicrobial peptide can restore wild-type resistance to infection in immunodeficient *Drosophila* mutants, *Proceedings of the National Academy of Sciences USA* 99:2152–2157 (2002).

WHAT IF? Even if a particular antimicrobial peptide showed no beneficial effect in such an experiment, why might it still be beneficial to flies?

Innate Immunity of Vertebrates

Among vertebrates, innate immune defenses coexist with the more recently evolved system of adaptive immunity. Because most of the recent discoveries regarding vertebrate innate immunity have come from studies of mice and humans, we'll focus here on mammals. We'll consider the innate defenses that are similar to those found among invertebrates: barrier defenses, phagocytosis, and antimicrobial peptides. We'll also examine some unique aspects of vertebrate innate immunity, such as natural killer cells, interferons, and the inflammatory response.

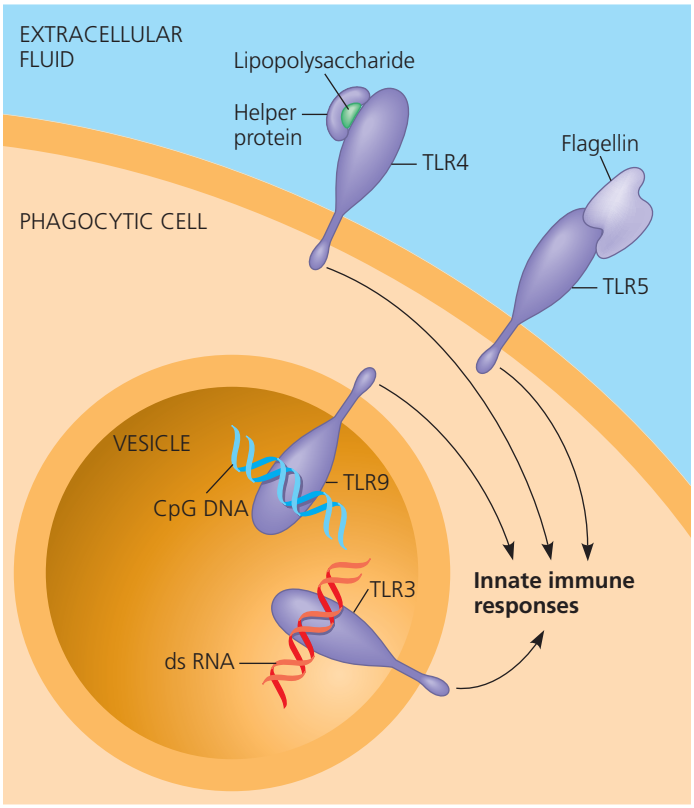
Barrier Defenses

In mammals, epithelial tissues block the entry of many pathogens. These barrier defenses include not only the skin but also the mucous membranes lining the digestive, respiratory, urinary, and reproductive tracts. Certain cells of the mucous membranes produce *mucus*, a viscous fluid that enhances defenses by trapping microbes and other particles. In the trachea, ciliated epithelial cells sweep mucus and any entrapped microbes upward, helping prevent infection of the lungs. Saliva, tears, and mucous secretions that bathe various exposed epithelia provide a washing action that also inhibits colonization by fungi and bacteria.

Beyond their physical role in inhibiting microbial entry, body secretions create an environment that is hostile to many microbes. Lysozyme in tears, saliva, and mucous secretions destroys the cell walls of susceptible bacteria as they enter the openings around the eyes or the upper respiratory tract. Microbes in food or water and those in swallowed mucus must also contend with the acidic environment of the stomach, which kills most of them before they can enter the intestines. Similarly, secretions from oil and sweat glands give human skin a pH ranging from 3 to 5, acidic enough to prevent the growth of many bacteria.

Cellular Innate Defenses

Pathogens entering the mammalian body are subject to phagocytosis. Phagocytic cells detect fungal or bacterial components using several types of receptors, some of which are very similar to the Toll receptor of insects. Each mammalian **Toll-like receptor (TLR)** binds to fragments of molecules characteristic of a set of pathogens **(Figure 43.6)**. For example, TLR3, on the inner surface of vesicles formed by endocytosis, is the sensor for double-stranded RNA, a form of nucleic acid characteristic of certain viruses. Similarly, TLR4, located on immune cell plasma membranes, recognizes lipopolysaccharide, a type of molecule found on the surface of many bacteria; and TLR5 recognizes flagellin, the main protein of bacterial flagella. In each case, the recognized macromolecule is normally absent from the vertebrate body and is an essential component of certain groups of pathogens.



▲ **Figure 43.6 TLR signaling.** Each mammalian Toll-like receptor (TLR) recognizes a molecular pattern characteristic of a group of pathogens. Lipopolysaccharide, flagellin, CpG DNA (DNA containing unmethylated CG sequences), and double-stranded (ds) RNA are all found in bacteria, fungi, or viruses, but not in animal cells. Together with other recognition and response factors, TLR proteins trigger internal innate immune defenses.

? *Some TLR proteins are on the cell surface, whereas others are inside vesicles. Suggest a possible benefit of this distribution.*

After detecting invading pathogens, a phagocytic cell engulfs them, trapping them in a vacuole. The vacuole then fuses with a lysosome (see Figure 43.3), leading to destruction of the invaders in two ways. First, gases produced in the lysosome poison the engulfed pathogens. Second, lysozyme and other enzymes in the lysosome degrade the components of the pathogens.

The two main types of phagocytic cells in the mammalian body are neutrophils and macrophages. **Neutrophils**, which circulate in the blood, are attracted by signals from infected tissues and then engulf and destroy the infecting pathogens. **Macrophages** ("big eaters"), like the one shown in Figure 43.1, are larger phagocytic cells. Some migrate throughout the body, whereas others reside permanently in organs and tissues where they are likely to encounter pathogens. For example, some macrophages are located in the spleen, where pathogens in the blood become trapped.

Two other types of phagocytic cells—dendritic cells and eosinophils—provide additional functions in innate defense. **Dendritic cells** mainly populate tissues, such as skin, that contact the environment. They stimulate adaptive immunity

against pathogens they encounter and engulf, as we'll explore shortly. *Eosinophils*, often found beneath mucosal surfaces, have low phagocytic activity but are important in defending against multicellular invaders, such as parasitic worms. Upon encountering such parasites, eosinophils discharge destructive enzymes.

Cellular innate defenses in vertebrates also involve **natural killer cells**. These cells circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells. Natural killer cells do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.

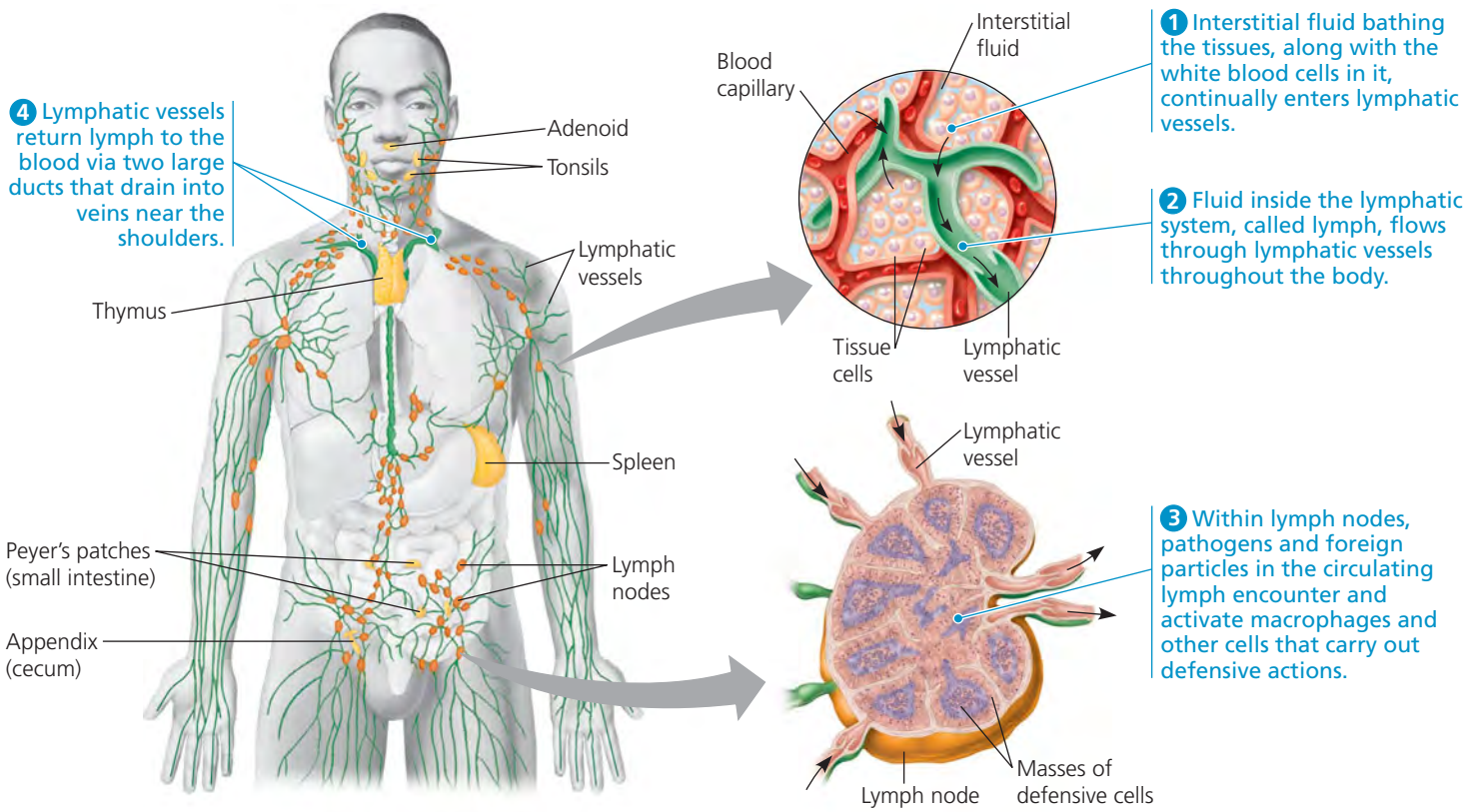
Many cellular innate defenses of vertebrates involve the lymphatic system, a network that distributes the fluid called lymph throughout the body **(Figure 43.7)**. Some macrophages reside in the structures called lymph nodes, where they engulf pathogens that have flowed from the interstitial fluid into the lymph. Dendritic cells reside outside the lymphatic system but migrate to lymph nodes after interaction with pathogens. Within the lymph nodes, dendritic cells interact with other immune cells, stimulating adaptive immunity.

Antimicrobial Peptides and Proteins

In mammals, pathogen recognition triggers the production and release of a variety of peptides and proteins that attack pathogens or impede their reproduction. Some of these defense molecules function like the antimicrobial peptides of insects, damaging broad groups of pathogens by disrupting membrane integrity. Others, including the interferons and complement proteins, are unique to vertebrate immune systems.

Interferons are proteins that provide innate defense by interfering with viral infections. Virus-infected body cells secrete interferons, which induce nearby uninfected cells to produce substances that inhibit viral reproduction. In this way, interferons limit the cell-to-cell spread of viruses in the body, helping control viral infections such as colds and influenza. Some white blood cells secrete a different type of interferon that helps activate macrophages, enhancing their phagocytic ability. Pharmaceutical companies now use recombinant DNA technology to mass-produce interferons to help treat certain viral infections, such as hepatitis C.

The infection-fighting **complement system** consists of roughly 30 proteins in blood plasma. These proteins circulate in an inactive state and are activated by substances on the surface of many microbes. Activation results in a cascade of biochemical reactions that can lead to lysis (bursting) of invading cells. The complement system also functions in the inflammatory response, our next topic, as well as in the adaptive defenses discussed later in the chapter.



▲ **Figure 43.7 The human lymphatic system.** The lymphatic system consists of lymphatic vessels (shown in green), through which lymph travels, and structures that trap foreign substances. These structures include lymph nodes (orange) and lymphoid organs (yellow): the adenoids, tonsils, spleen, Peyer's patches, and appendix. Steps 1–4 trace the flow of lymph and illustrate the critical role of lymph nodes in activating adaptive immunity. (See also p. 909 for a description of the relationship between the lymphatic and circulatory systems.)

Inflammatory Response

The pain and swelling that alert you to a splinter under your skin are the result of a local **inflammatory response**, the changes brought about by signaling molecules released upon injury or infection **(Figure 43.8)**. One important inflammatory signaling molecule is **histamine**, which is stored in the granules (vesicles) of **mast cells**, found in connective tissue. Histamine released at sites of damage triggers nearby blood vessels to dilate and become more permeable. Activated macrophages and neutrophils discharge **cytokines**, signaling molecules that enhance an immune response. These cytokines promote blood flow to the site of injury or infection. The increase in local blood supply causes the redness and increased skin temperature typical of the inflammatory response (from the Latin *inflammare*, to set on fire). Blood-engorged capillaries leak fluid into neighboring tissues, causing swelling.

During inflammation, cycles of signaling and response transform the site. Activated complement proteins promote further release of histamine, attracting more phagocytic cells that enter injured tissues (see Figure 43.8) and carry out additional phagocytosis. At the same time, enhanced blood flow to the site helps deliver antimicrobial peptides. The result is an accumulation of *pus*, a fluid rich in white blood cells, dead pathogens, and cell debris from damaged tissue.

A minor injury or infection causes a local inflammatory response, but severe tissue damage or infection may lead to a response that is systemic (throughout the body). Cells in injured or infected tissue often secrete molecules that stimulate the release of additional neutrophils from the bone marrow. In a severe infection, such as meningitis or appendicitis, the number of white blood cells in the blood may increase several-fold within a few hours.

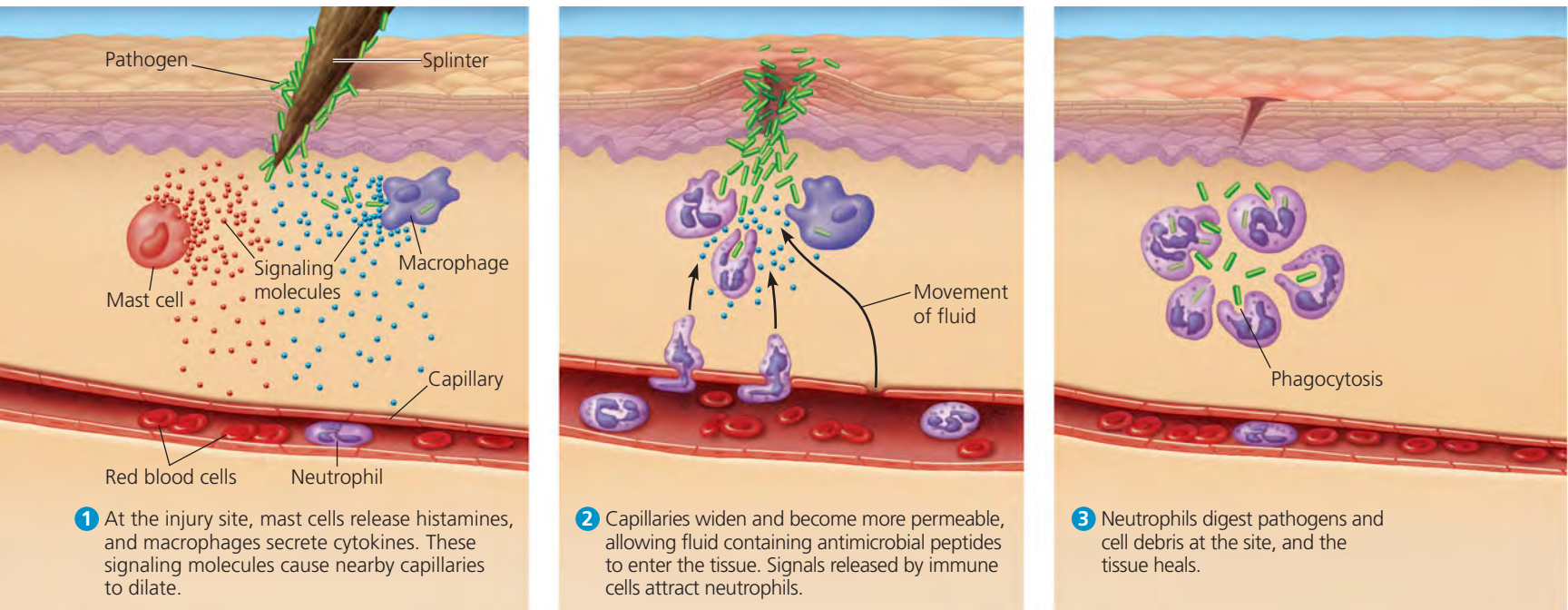
Another systemic inflammatory response is fever. In response to certain pathogens, substances released by activated macrophages cause the body's thermostat to reset to a higher temperature (see Chapter 40). The benefits of the resulting fever are still a subject of debate. One of several competing hypotheses is that an elevated body temperature may enhance phagocytosis and, by speeding up chemical reactions, accelerate tissue repair.

Certain bacterial infections can induce an overwhelming systemic inflammatory response, leading to a life-threatening condition called *septic shock*. Characterized by very high fever, low blood pressure, and poor blood flow through capillaries, septic shock occurs most often in the very old and the very young. It is fatal in more than one-third of cases and kills more than 90,000 people each year in the United States alone.

Chronic (ongoing) inflammation can also threaten human health. For example, millions of individuals worldwide suffer from Crohn's disease and ulcerative colitis, often debilitating disorders in which an unregulated inflammatory response disrupts intestinal function.

Evasion of Innate Immunity by Pathogens

Adaptations have evolved in some pathogens that enable them to avoid destruction by phagocytic cells. For example, the outer capsule that surrounds certain bacteria interferes with molecular recognition and phagocytosis. One such bacterium, *Streptococcus pneumoniae*, played a critical role in the discovery that DNA can convey genetic information (see



▲ **Figure 43.8 Major events in a local inflammatory response.**

Figure 16.2). Some bacteria, after being engulfed by a host cell, resist breakdown within lysosomes. An example is the bacterium that causes tuberculosis (TB). Rather than being destroyed within host cells, this bacterium grows and reproduces, effectively hidden from the body's innate immune defenses. These and other mechanisms that prevent destruction by the innate immune system make certain fungi and bacteria substantial pathogenic threats. Indeed, TB kills more than a million people a year worldwide.

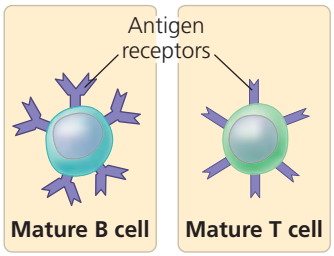
CONCEPT CHECK 43.1

1. Although pus is often seen simply as a sign of infection, it is also an indicator of immune defenses in action. Explain.
2. **MAKE CONNECTIONS** How do the molecules that activate the vertebrate TLR signal transduction pathway differ from the ligands in most other pathways, such as those shown in Concept 11.2 (pp. 210–214)?
3. **WHAT IF?** Suppose humans were the major host for a bacterial species. What temperature would you predict would be optimal for growth of this species? Explain.

For suggested answers, see Appendix A.

CONCEPT 43.2

In adaptive immunity, receptors provide pathogen-specific recognition



Vertebrates are unique in having adaptive immunity in addition to innate immunity. The adaptive response relies on T cells and B cells, which are types of white blood cells called **lymphocytes**. Like all blood cells, lymphocytes originate from stem cells in the bone marrow. Some lymphocytes migrate from the bone marrow to the **thymus**, an organ in the thoracic cavity above the heart (see Figure 43.7). These lymphocytes mature into **T cells**. Lymphocytes that remain and mature in the bone marrow develop as **B cells**. (Lymphocytes of a third type remain in the blood and become the natural killer cells active in innate immunity.)

Any substance that elicits a response from a B cell or T cell is called an **antigen**. In adaptive immunity, recognition occurs when a B cell or T cell binds to an antigen, such as a bacterial or viral protein, via a protein called an **antigen receptor**. An antigen receptor is specific enough to bind to just one part of one molecule from a particular pathogen, such as a species of bacteria or strain of virus. Although the cells of the immune system produce millions of different antigen receptors, all of the antigen receptors made by a single B or T cell are identical. Infection by a virus, bacterium, or other pathogen triggers activation of B and T cells with antigen receptors specific for parts of that pathogen. B and T cells are shown here with only a few antigen receptors, but there are actually about 100,000 antigen receptors on the surface of a single B or T cell.

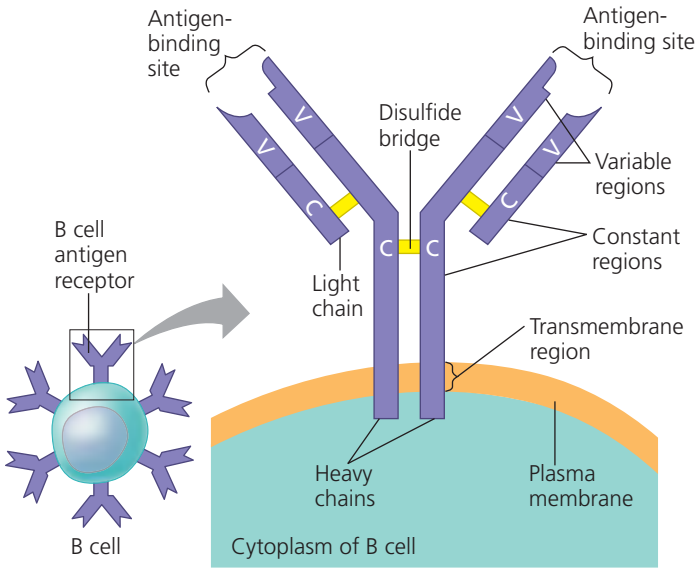
Antigens are usually foreign and are typically large molecules, either proteins or polysaccharides. Many antigens protrude from the surface of foreign cells or viruses. Other antigens, such as toxins secreted by bacteria, are released into the extracellular fluid.

The small, accessible portion of an antigen that binds to an antigen receptor is called an **epitope**, or *antigenic determinant*. An example is a group of amino acids in a particular protein. A single antigen usually has several different epitopes, each binding a receptor with a different specificity. Because all antigen receptors produced by a single B cell or T cell are identical, they bind to the same epitope. Each B cell or T cell thus displays *specificity* for a particular epitope, enabling it to respond to any pathogen that produces molecules containing that same epitope.

The antigen receptors of B cells and T cells have similar components, but they encounter antigens in different ways. We'll consider the two processes in turn.

Antigen Recognition by B Cells and Antibodies

Each B cell antigen receptor is a Y-shaped molecule consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains**, with disulfide bridges linking the chains together **(Figure 43.9)**. A transmembrane region near one end of each heavy chain anchors the receptor in the cell's plasma membrane. A short tail region at the end of the heavy chain extends into the cytoplasm.



▲ **Figure 43.9 The structure of a B cell antigen receptor.**

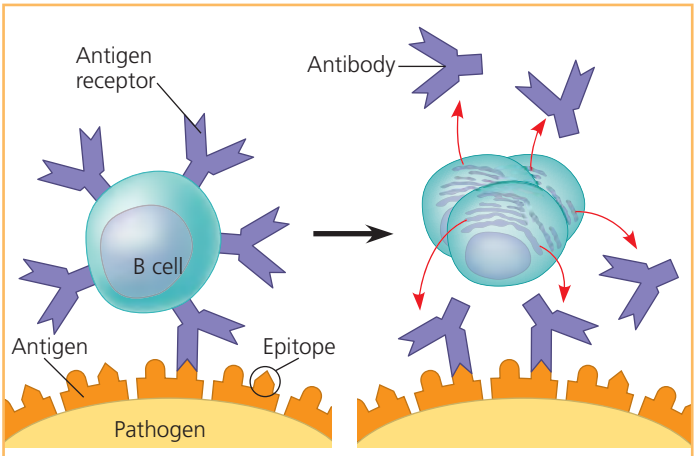
The light and heavy chains each have a *constant (C) region*, where amino acid sequences vary little among the receptors on different B cells. The C region includes the cytoplasmic tail and transmembrane region of the heavy chain and all of the disulfide bridges. Within the two tips of the Y shape, the light and heavy chains each have a *variable (V) region*, so named because its amino acid sequence varies extensively from one B cell to another. Together, parts of a heavy-chain V region and a light-chain V region form an asymmetrical binding site for an antigen. As shown in Figure 43.9, each B cell antigen receptor has two identical antigen-binding sites.

The binding of a B cell antigen receptor to an antigen is an early step in B cell activation, leading eventually to formation of cells that secrete a soluble form of the receptor **(Figure 43.10a)**. This secreted protein is called an **antibody**, or **immunoglobulin (Ig)**. Antibodies have the same Y-shaped organization as B cell antigen receptors, but they are secreted rather than membrane bound. It is the antibodies, rather than the B cells themselves, that actually help defend against pathogens. Antibodies have distinct functions, as we'll see later.

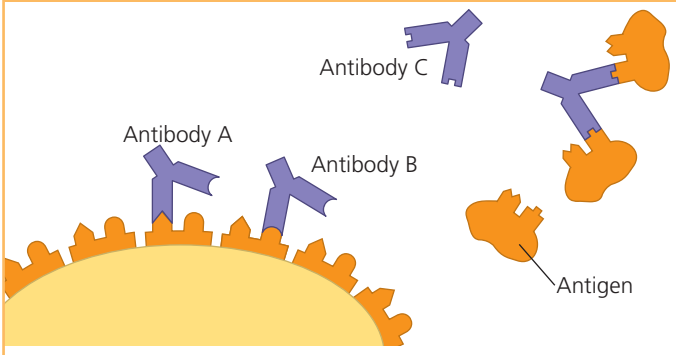
The antigen-binding site of a membrane-bound receptor or antibody has a unique shape that provides a lock-and-key fit for a particular epitope. Many noncovalent bonds between an epitope and the binding surface provide a stable and specific interaction. Differences in the amino acid sequences of variable regions provide the variation in binding surfaces that enables this highly specific binding.

B cell antigen receptors and antibodies bind to intact antigens in the blood and lymph. As illustrated in **Figure 43.10b** for antibodies, they can bind to antigens on the surface of pathogens or free in body fluids. The antigen receptors of T cells function quite differently, as we'll see next.

▼ Figure 43.10 Antigen recognition by B cells and antibodies.



(a) B cell antigen receptors and antibodies. An antigen receptor of a B cell binds to an epitope, a particular part of an antigen. Following binding, the B cell gives rise to cells that secrete a soluble form of the antigen receptor. This soluble receptor, called an antibody, is specific for the same epitope as the original B cell.



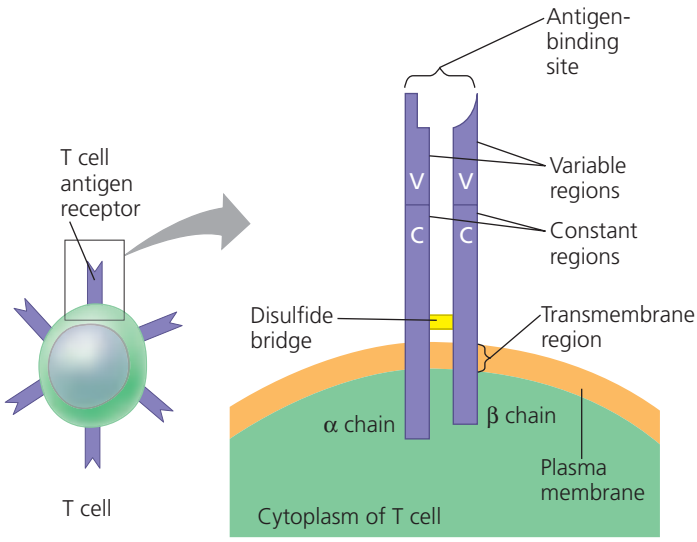
(b) Antigen receptor specificity. Different antibodies can recognize distinct epitopes on the same antigen. Furthermore, antibodies can recognize free antigens as well as antigens on a pathogen's surface.

MAKE CONNECTIONS *The interactions depicted here involve a highly specific binding between antigen and receptor, as shown in Figure 5.19 (p. 81). How is this similar to the enzyme-substrate interaction shown in Figure 8.14 (p. 154)?*

Antigen Recognition by T Cells

For a T cell, the antigen receptor consists of two different polypeptide chains, an *α chain* and a *β chain*, linked by a disulfide bridge **(Figure 43.11)**. Near the base of the T cell antigen receptor (often called simply a T cell receptor) is a transmembrane region that anchors the molecule in the cell's plasma membrane. At the outer tip of the molecule, the variable (V) regions of α and β chains together form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

Although T cell and B cell antigen receptors have many features in common, they function in fundamentally different ways. Whereas the antigen receptors of B cells bind to epitopes of intact antigens circulating in body fluids, those of

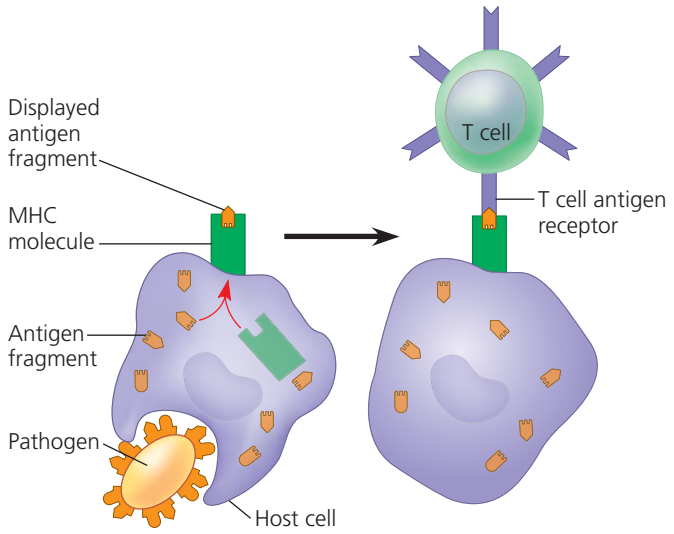


▲ Figure 43.11 The structure of a T cell antigen receptor.

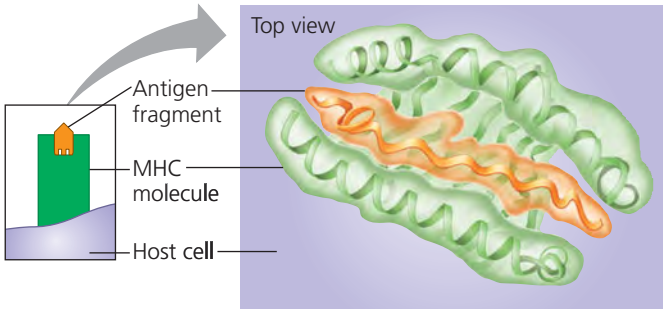
T cells bind only to fragments of antigens that are displayed, or *presented*, on the surface of host cells. The host protein that displays the antigen fragment on the cell surface is called an **MHC (major histocompatibility complex) molecule**.

Recognition of protein antigens by T cells begins when a pathogen or part of a pathogen either infects or is taken in by a host cell **(Figure 43.12a)**. Inside the host cell, enzymes in the cell cleave the antigen into smaller peptides. Each peptide, called an *antigen fragment*, then binds to an MHC molecule inside the cell. Movement of the MHC molecule and bound antigen fragment to the cell surface results in **antigen presentation**, the display of the antigen fragment in an exposed groove of the MHC protein. **Figure 43.12b** shows a close-up view of antigen presentation, which advertises the fact that a host cell contains a foreign substance. If the cell displaying an antigen fragment encounters a T cell with the right specificity, the antigen receptor on the T cell can bind to both the antigen fragment and the MHC molecule. This interaction of an MHC molecule, an antigen fragment, and an antigen receptor is necessary for a T cell to participate in an adaptive immune response, as we'll see later.

▼ Figure 43.12 Antigen recognition by T cells.



(a) Antigen recognition by a T cell. Inside the host cell, an antigen fragment from a pathogen binds to an MHC molecule and is brought up to the cell surface, where it is displayed. The combination of MHC molecule and antigen fragment is recognized by a T cell.



(b) A closer look at antigen presentation. As shown in this ribbon model, the top of the MHC molecule cradles an antigen fragment, like a bun holding a hot dog. An MHC molecule can display many different antigen fragments, but the antigen receptor of a T cell is specific for a single antigen fragment.

B Cell and T Cell Development

Now that you know how B cells and T cells recognize antigens, let's consider four major characteristics of adaptive immunity. First, there is an immense diversity of lymphocytes and receptors, enabling the immune system to detect pathogens never before encountered. Second, adaptive immunity normally has self-tolerance, the lack of reactivity against an animal's own molecules and cells. Third, cell proliferation triggered by activation greatly increases the number of B and T cells specific for an antigen. Fourth, there is a stronger and more rapid response to an antigen encountered previously, due to a feature known as *immunological memory*.

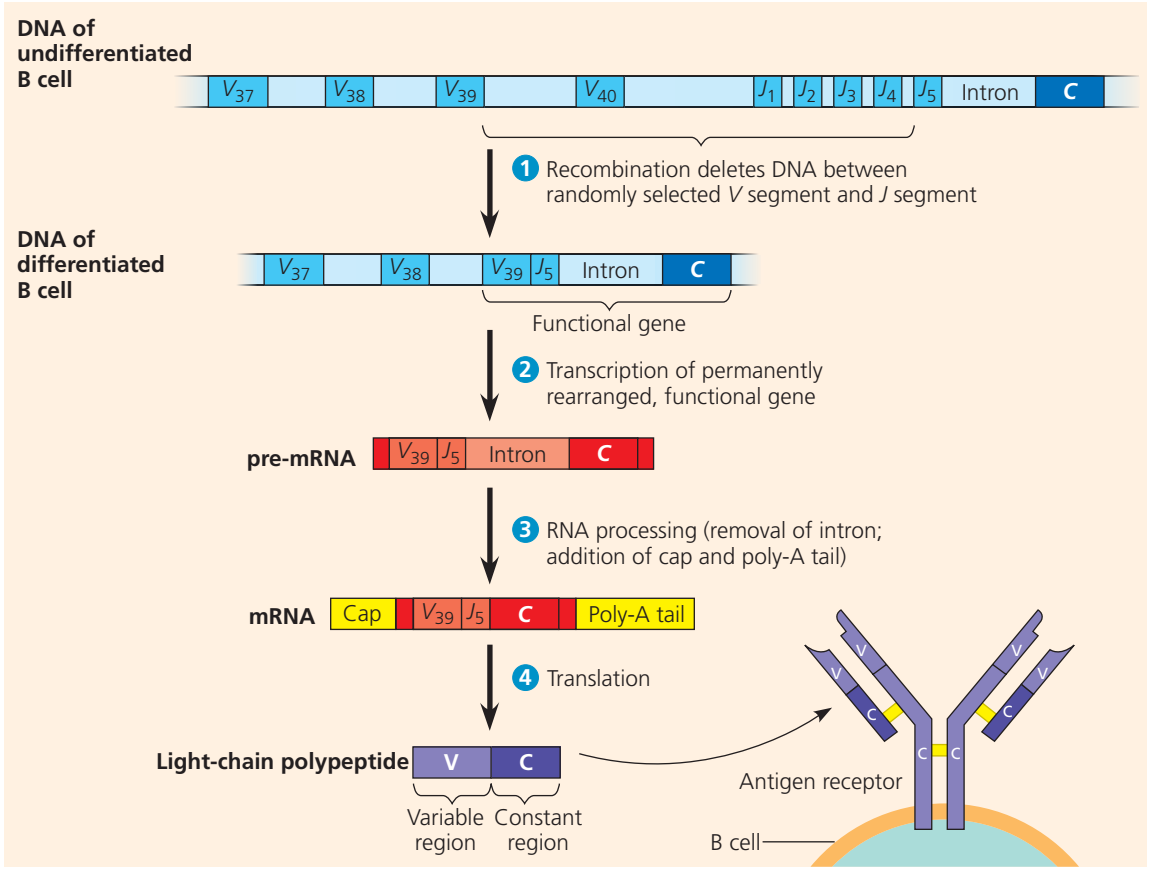
Receptor diversity and self-tolerance arise as a lymphocyte matures. Proliferation of cells and the formation of immunological memory occur later, after a mature lymphocyte encounters and binds to a specific antigen. We'll consider these four characteristics in the order in which they develop.

Generation of B and T Cell Diversity

Each person makes more than 1 million different B cell antigen receptors and 10 million different T cell antigen receptors. Yet there are only about 20,000 protein-coding genes in the human genome. How, then, do we generate such remarkable diversity in antigen receptors? The answer lies in combinations. Think of selecting a car with a choice of three interior colors and six exterior colors. There are 18 (3×6) color combinations to consider. Similarly, by combining variable elements, the immune system assembles many different receptors from a much smaller collection of parts.

To understand the origin of receptor diversity, let's consider an immunoglobulin (Ig) gene that encodes the light chain of both secreted antibodies (immunoglobulins) and membrane-bound B cell antigen receptors. Although we'll analyze only a single Ig light-chain gene, all B and T cell antigen receptor genes undergo very similar transformations.

The capacity to generate diversity is built into the structure of Ig genes. A receptor light chain is encoded by three gene segments: a variable (*V*) segment, a joining (*J*) segment, and a constant (*C*) segment. The *V* and *J* segments together encode the variable region of the receptor chain, while the *C* segment encodes the constant region. The light-chain gene contains a single *C* segment, 40 different *V* segments, and 5 different *J* segments. These alternative copies of the *V* and *J* segments are arranged within the gene in a



◀ Figure 43.13 Immunoglobulin (antibody) gene rearrangement. The joining of randomly selected *V* and *J* gene segments (V_{39} and J_5 in this example) results in a functional gene that encodes the light-chain polypeptide of a B cell antigen receptor. Transcription, splicing, and translation result in a light chain that combines with a polypeptide produced from an independently rearranged heavy-chain gene to form a functional receptor. Mature B cells (and T cells) are exceptions to the generalization that all nucleated cells in the body have exactly the same DNA.

MAKE CONNECTIONS

Both alternative splicing (see Figure 18.13 on p. 363) and joining of V and J segments by recombination generate diverse gene products from a limited set of gene segments. How do these processes differ?

series **(Figure 43.13)**. Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 different ways (40 V × 5 J × 1 C). The number of different heavy-chain combinations is even greater, resulting in even more diversity.

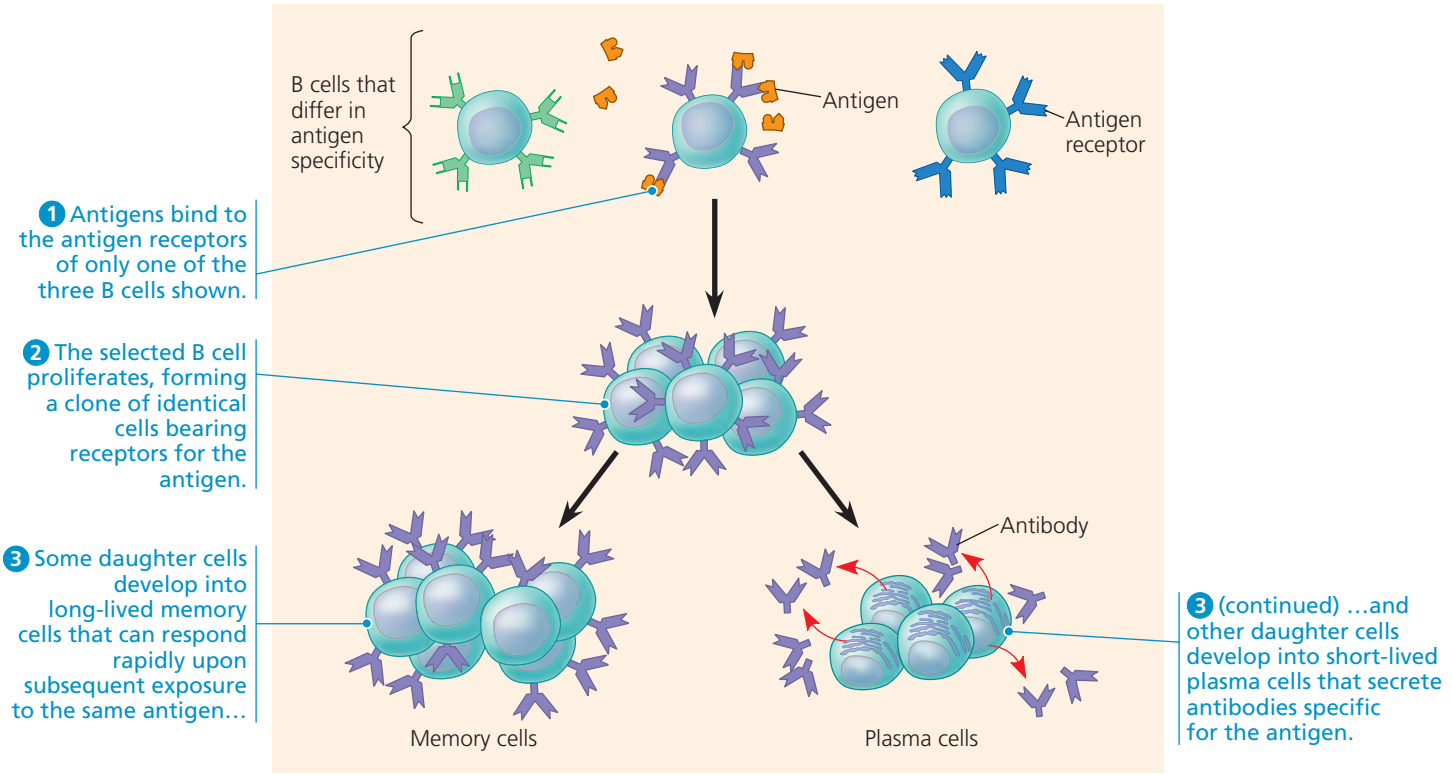
Assembling a functional Ig gene requires rearranging the DNA. Early in B cell development, an enzyme complex called *recombinase* links one light-chain *V* gene segment to one *J* gene segment. This recombination event eliminates the long stretch of DNA between the segments, forming a single exon that is part *V* and part *J*. Because there is only an intron between the *J* and *C* DNA segments, no further DNA rearrangement is required. Instead, the *J* and *C* segments of the RNA transcript will be joined when splicing removes the intervening RNA (see Figure 17.11 to review RNA splicing).

Recombinase acts randomly, linking any one of the 40 *V* gene segments to any one of the 5 *J* gene segments. Heavy-chain genes undergo a similar rearrangement. In any given cell, however, only one allele of a light-chain gene and one allele of a heavy-chain gene are rearranged. Furthermore, the rearrangements are permanent and are passed on to the daughter cells when the lymphocyte divides.

After both the light- and heavy-chain genes have rearranged, antigen receptors can be synthesized. The rearranged genes are transcribed, and the transcripts are processed for translation. Following translation, the light chain and heavy chain assemble together, forming an antigen receptor (see Figure 43.13). Each pair of randomly rearranged heavy and light chains results in a different antigen-binding site. For the total population of B cells in a human body, the number of such combinations has been calculated as 3.5×10^6. Furthermore, mutations introduced during *VJ* recombination add additional variation, making the number of possible antigen-binding specificities even greater.

Origin of Self-Tolerance

How does adaptive immunity distinguish self from nonself? Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the organism's own molecules. If these self-reactive lymphocytes were not eliminated or inactivated, the immune system could not distinguish self from nonself and would attack body proteins, cells, and tissues. Instead, as lymphocytes mature in the bone marrow or thymus, their antigen receptors are tested for self-reactivity. Some B and T cells with receptors specific for the body's own molecules are destroyed by *apoptosis*, which is a programmed cell death (see Chapter 11). The remaining self-reactive lymphocytes are typically rendered nonfunctional, leaving only those that react to foreign molecules. Since the body normally lacks mature lymphocytes that can react against its own components, the immune system is said to exhibit *self-tolerance*.



▲ **Figure 43.14 Clonal selection.** This figure illustrates clonal selection, using B cells as an example. In response to a specific antigen and to immune cell signals (not shown), one B cell divides and forms a clone of cells. The remaining B cells, which have antigen receptors specific for other antigens, do not respond. The clone of cells formed by the selected B cell gives rise to memory B cells and antibody-secreting plasma cells. T cells also undergo clonal selection, generating memory T cells and effector T cells (cytotoxic T cells and helper T cells).

Proliferation of B Cells and T Cells

Despite the enormous variety of antigen receptors, only a tiny fraction are specific for a given epitope. So how is adaptive immunity so effective? To begin with, an antigen is presented to a steady stream of lymphocytes in the lymph nodes (see Figure 43.7) until a match is made. A successful match then triggers changes in cell number and activity for the lymphocyte to which an antigen has bound.

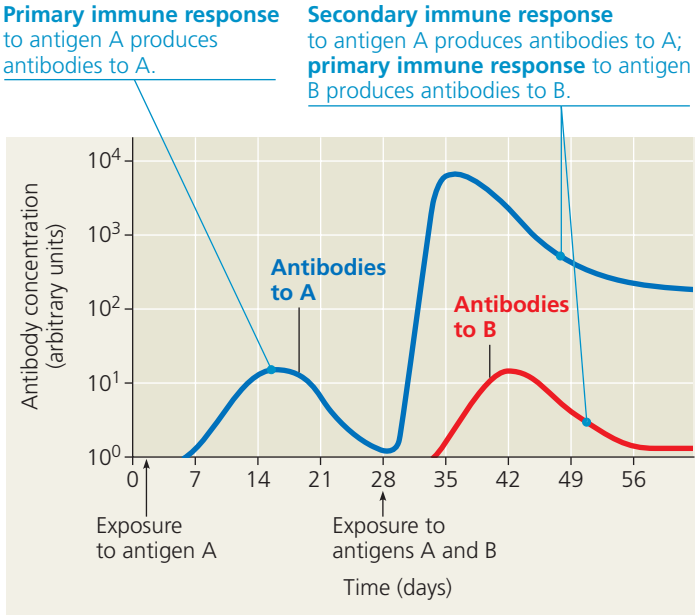
The binding of an antigen receptor to an epitope initiates events that activate the lymphocyte. Once activated, a B cell or T cell undergoes multiple cell divisions. For each activated cell, the result of this proliferation is a clone, a population of cells that are identical to the original cell. Some cells from this clone become **effector cells**, short-lived cells that take effect immediately against the antigen and any pathogens producing that antigen. The effector forms of B cells are plasma cells, which secrete antibodies. The effector forms of T cells are helper T cells and cytotoxic T cells, whose roles we'll explore in Concept 43.3. The remaining cells in the clone become **memory cells**, long-lived cells that can give rise to effector cells if the same antigen is encountered later in the animal's life.

Figure 43.14 summarizes the proliferation of a lymphocyte into a clone of cells in response to binding to an antigen, using B cells as an example. This process is called **clonal selection** because an encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells specific for a particular epitope.

Immunological Memory

Immunological memory is responsible for the long-term protection that a prior infection or vaccination provides against many diseases, such as chickenpox. This type of protection was noted almost 2,400 years ago by the Greek historian Thucydides. He observed that individuals who had recovered from the plague could safely care for those who were sick or dying, "for the same man was never attacked twice—never at least fatally."

Prior exposure to an antigen alters the speed, strength, and duration of the immune response. The production of effector cells from a clone of lymphocytes during the first exposure to an antigen is the basis for the **primary immune response**. The primary response peaks about 10–17 days after the initial exposure. During this time, selected B cells and T cells give rise to their effector forms. If an individual is exposed again to the same antigen, the response is faster (typically peaking only 2–7 days after exposure), of greater magnitude, and more prolonged. This is the **secondary immune response**, a hallmark of adaptive, or acquired, immunity. Because selected B cells give



▲ **Figure 43.15 The specificity of immunological memory.** Long-lived memory cells generated in the primary response to antigen A give rise to a heightened secondary response to the same antigen, but do not affect the primary response to a different antigen (B).

rise to antibody-secreting effector cells, measuring the concentrations of specific antibodies in blood over time distinguishes the primary and secondary immune responses **(Figure 43.15)**.

The secondary immune response relies on the reservoir of T and B memory cells generated following initial exposure to an antigen. Because these cells are long-lived, they provide the basis for immunological memory, which can span many decades. (Effector cells have much shorter life spans, which is why the immune response diminishes after an infection is overcome.) If an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of clones of thousands of effector cells also specific for that antigen, thus generating a greatly enhanced immune defense.

Although the processes for antigen recognition, clonal selection, and immunological memory are similar for B cells and T cells, these two classes of lymphocytes fight infection in different ways and in different settings, as we'll explore next.

CONCEPT CHECK 43.2

1. **DRAW IT** Sketch a B cell antigen receptor. Label the V and C regions of the light and heavy chains. Label the antigen-binding sites, disulfide bridges, and transmembrane region. Where are these features located relative to the V and C regions?
2. Explain two advantages of having memory cells when a pathogen is encountered for a second time.
3. **WHAT IF?** If both copies of a light-chain gene and a heavy-chain gene recombined in each (diploid) B cell, how would this affect B cell development?

For suggested answers, see Appendix A.

CONCEPT 43.3

Adaptive immunity defends against infection of body fluids and body cells

Having considered how clones of lymphocytes arise, we now explore how these cells help fight infections and minimize damage by pathogens. The activities of B and T lymphocytes produce a humoral immune response and a cell-mediated immune response. The **humoral immune response** occurs in the blood and lymph, which were long ago called body humors (fluids). In the humoral response, antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph. In the **cell-mediated immune response**, specialized T cells destroy infected host cells. Both responses include a primary immune response and a secondary immune response, with memory cells enabling the secondary response.

Helper T Cells: A Response to Nearly All Antigens

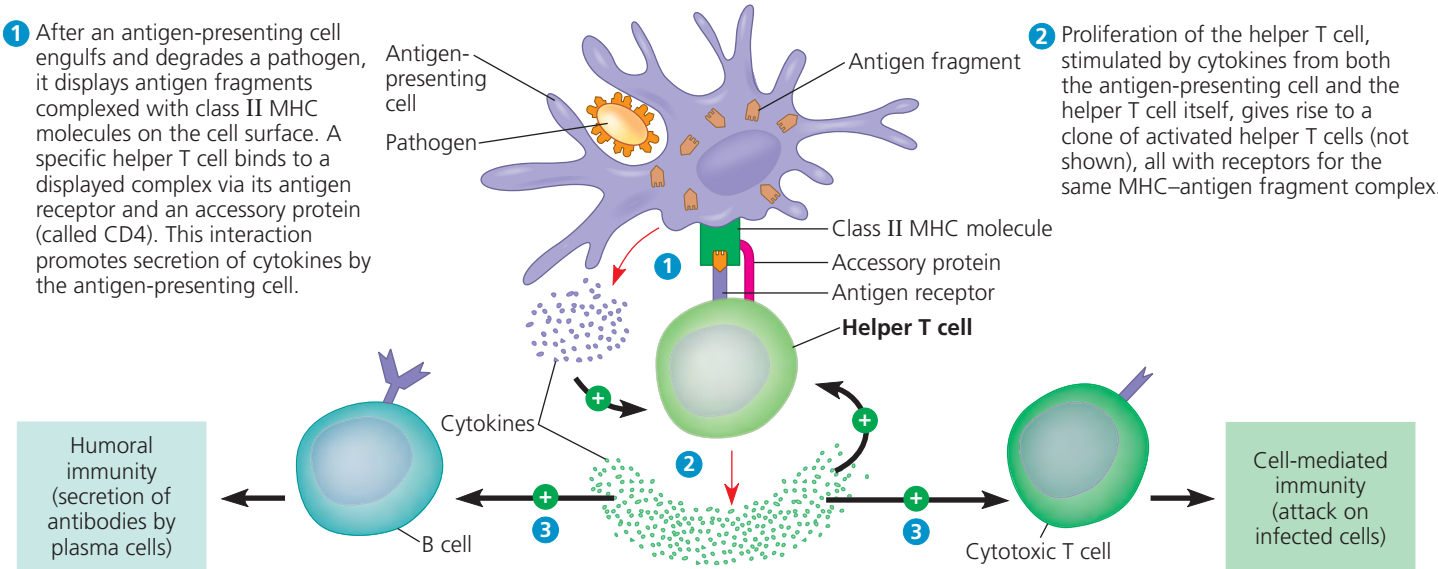
A type of T cell called a **helper T cell** triggers both the humoral and cell-mediated immune responses. Helper T cells themselves do not carry out those responses. Instead, signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells.

Two requirements must be met for a helper T cell to activate adaptive immune responses. First, a foreign molecule must be present that can bind specifically to the antigen receptor of the T cell. Second, this antigen must be displayed on the surface of an **antigen-presenting cell**. The antigen-presenting cell can be a dendritic cell, macrophage, or B cell.

When host cells are infected, they too display antigens on their surface. What then distinguishes an antigen-presenting cell? The answer lies in the existence of two classes of MHC molecules. Most body cells have only class I MHC molecules, but antigen-presenting cells have both class I and class II MHC molecules. The class II molecules provide a molecular signature by which an antigen-presenting cell is recognized.

A helper T cell and the antigen-presenting cell displaying its specific epitope have a complex interaction **(Figure 43.16)**. The antigen receptors on the surface of the helper T cell bind to the antigen fragment and to the class II MHC molecule displaying that fragment on the antigen-presenting cell. At the same time, an accessory protein on the helper T cell surface binds to the class II MHC molecule, helping keep the cells joined. As the two cells interact, signals in the form of cytokines are exchanged in both directions. For example, the cytokines secreted from a dendritic cell act in combination with the antigen to stimulate the helper T cell, causing it to produce its own set of cytokines. Also, extensive contact between the cell surfaces enables further information exchange.

The different types of antigen-presenting cells interact with helper T cells in distinct contexts. Antigen presentation



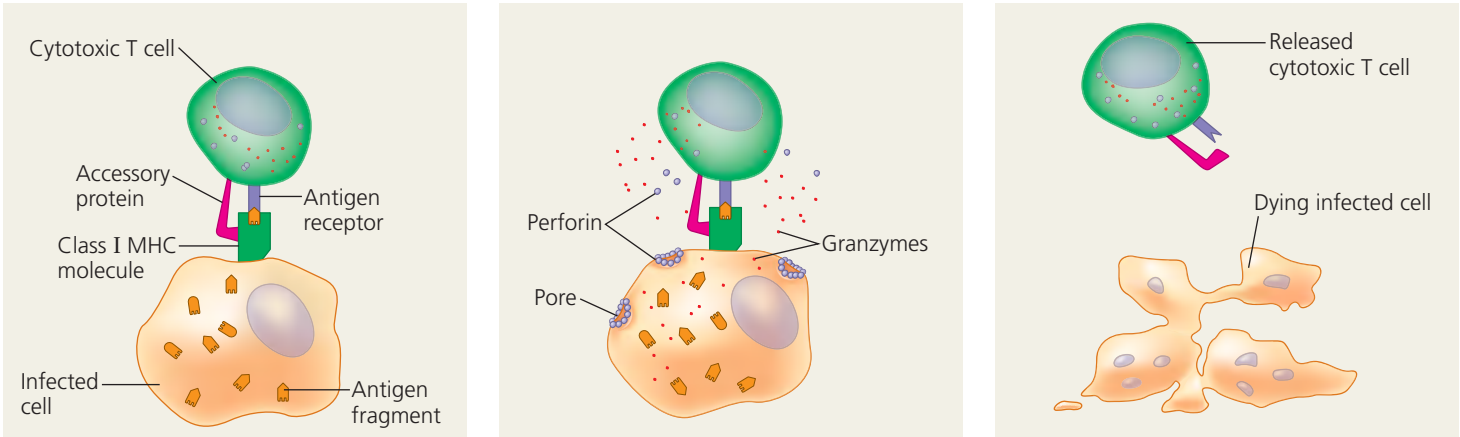
▲ Figure 43.16 The central role of helper T cells in humoral and cell-mediated immune responses. In this example, a helper T cell responds to a dendritic cell displaying a microbial antigen.

by a dendritic cell or macrophage activates a helper T cell. The helper T cell then proliferates, forming a clone of activated helper T cells. The B cells present antigens to *already* activated helper T cells, which in turn activate the B cells themselves. Activated helper T cells also help stimulate cytotoxic T cells, as we'll discuss next.

Cytotoxic T Cells: A Response to Infected Cells

In the cell-mediated immune response, **cytotoxic T cells** are the effector cells. The term *cytotoxic* refers to their use of toxic gene products to kill infected cells. To become active, they require signaling molecules from helper T cells as well as interaction with a cell that presents an antigen. Once activated, cytotoxic T cells can eliminate cells that are infected by viruses or other intracellular pathogens.

Fragments of foreign proteins produced in infected host cells associate with class I MHC molecules and are displayed on the cell surface, where they can be recognized by cytotoxic T cells **(Figure 43.17)**. As with helper T cells, cytotoxic T cells have an accessory protein that binds to the MHC molecule, helping keep the two cells in contact while the T cell is activated.



1 An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on an infected cell via its antigen receptor and an accessory protein (called CD8).

2 The T cell releases perforin molecules, which form pores in the infected cell membrane, and granzymes, enzymes that break down proteins. Granzymes enter the infected cell by endocytosis.

3 The granzymes initiate apoptosis within the infected cell, leading to fragmentation of the nucleus and cytoplasm and eventual cell death. The released cytotoxic T cell can attack other infected cells.

▲ Figure 43.17 The killing action of cytotoxic T cells on an infected host cell. An activated cytotoxic T cell releases molecules that make pores in an infected cell's membrane and enzymes that break down proteins, promoting the cell's death.

The targeted destruction of an infected host cell by a cytotoxic T cell involves the secretion of proteins that disrupt membrane integrity and trigger apoptosis (see Figure 43.17). The death of the infected cell not only deprives the pathogen of a place to reproduce, but also exposes cell contents to circulating antibodies, which mark them for disposal. After destroying an infected cell, the cytotoxic T cell can move on and kill other cells infected with the same pathogen.

B Cells and Antibodies: A Response to Extracellular Pathogens

The secretion of antibodies by clonally selected B cells is the hallmark of the humoral immune response. We'll explore how B cells become activated before investigating how antibodies function.

Activation of B Cells

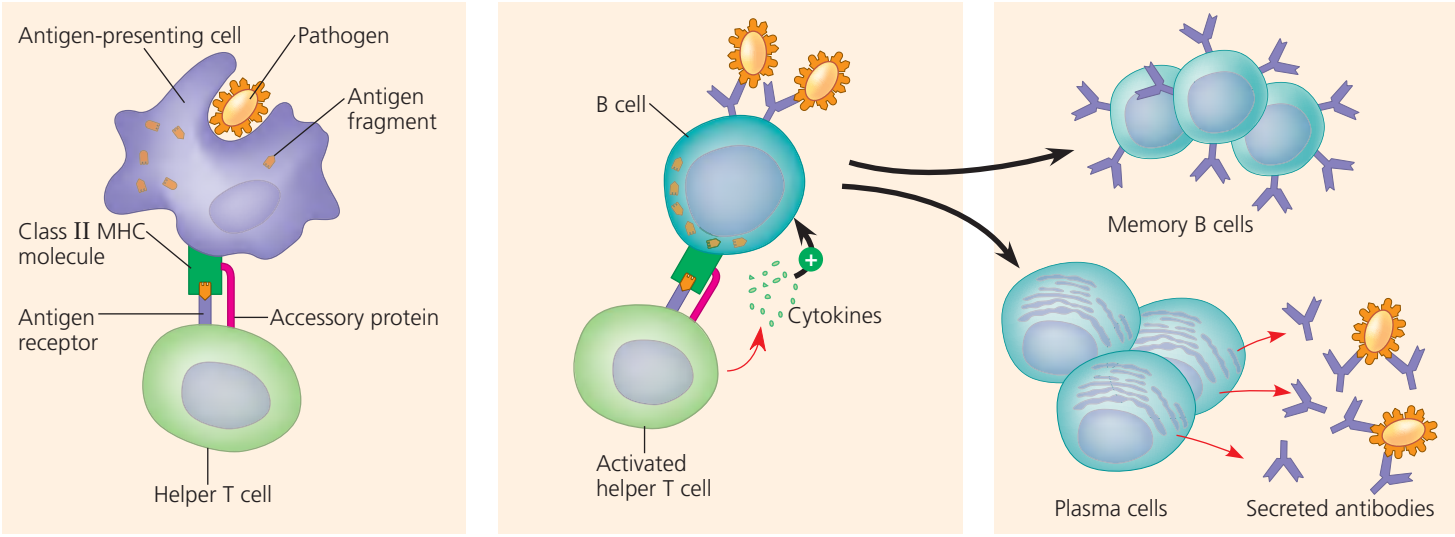
Activation of the humoral immune response typically involves B cells and helper T cells as well as proteins on the surface of pathogens. As depicted in **Figure 43.18**, B cell activation by an antigen is aided by cytokines secreted from helper T cells that have encountered the same antigen. Stimulated by both an antigen and cytokines, the B cell proliferates and differentiates into memory B cells and antibody-secreting effector cells called **plasma cells**.

The pathway for antigen processing and display in B cells differs from that in other antigen-presenting cells. A macrophage or dendritic cell can present fragments from a wide variety of protein antigens, whereas a B cell presents only the antigen to which it specifically binds. When an antigen first binds to receptors on the surface of a B cell, the cell takes in a few foreign molecules by receptor-mediated endocytosis (see Figure 7.22). The class II MHC protein of the B cell then presents an antigen fragment to a helper T cell. This direct cell-to-cell contact is usually critical to B cell activation (see step 2 in Figure 43.18).

B cell activation leads to a robust humoral immune response: An activated B cell gives rise to thousands of identical plasma cells. These plasma cells stop expressing a membrane-bound antigen receptor and begin producing and secreting antibodies (see step 3 in Figure 43.18). Each plasma cell secretes approximately 2,000 antibodies every second of the cell's 4- to 5-day life span. Furthermore, most antigens recognized by B cells contain multiple epitopes. An exposure to a single antigen therefore normally activates a variety of B cells, with different plasma cells producing antibodies directed against different epitopes on the common antigen.

Antibody Function

Antibodies do not kill pathogens, but by binding to antigens, they mark pathogens in various ways for inactivation or



1 After an antigen-presenting cell engulfs and degrades a pathogen, it displays an antigen fragment complexed with a class II MHC molecule. A helper T cell that recognizes the complex is activated with the aid of cytokines secreted from the antigen-presenting cell.

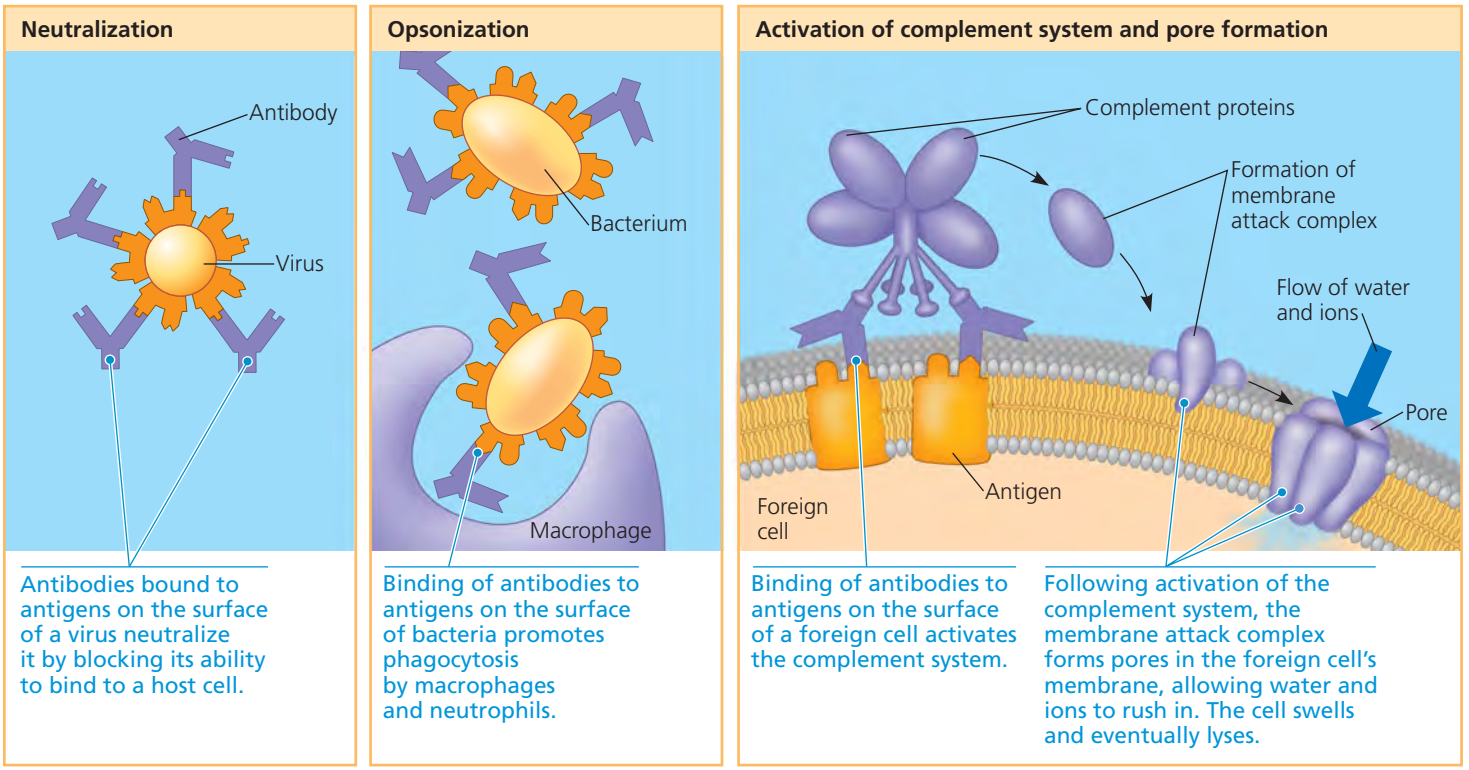
2 When a B cell with receptors for the same epitope internalizes the antigen, it displays an antigen fragment on the cell surface in a complex with a class II MHC molecule. An activated helper T cell bearing receptors specific for the displayed fragment binds to the B cell. This interaction, with the aid of cytokines from the T cell, activates the B cell.

3 The activated B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells. The secreted antibodies are specific for the same antigen that initiated the response.

▲ **Figure 43.18 Activation of a B cell in the humoral immune response.** Most protein antigens require activated helper T cells to trigger a humoral response. A macrophage (shown here) or a dendritic cell can activate a helper T cell, which in turn can activate a B cell to give rise to antibody-secreting plasma cells.

? *What function do cell-surface antigen receptors play for memory B cells?*

▼ Figure 43.19 Antibody-mediated mechanisms of antigen disposal.



destruction. In the simplest of these activities, *neutralization*, antibodies bind to viral surface proteins (**Figure 43.19**, left). The bound antibodies prevent infection of a host cell, thus neutralizing the virus. Similarly, antibodies sometimes bind to toxins released in body fluids, preventing the toxins from entering body cells. In another process, called *opsonization*, antibodies bound to antigens on bacteria present a readily recognized structure for macrophages or neutrophils and therefore increase phagocytosis (**Figure 43.19**, middle). Because each antibody has two antigen-binding sites, antibodies sometimes also facilitate phagocytosis by linking bacterial cells, virus particles, or other foreign substances into aggregates.

Antibodies sometimes work together with the proteins of the complement system to dispose of pathogens. (The name *complement* reflects the fact that these proteins increase the effectiveness of antibody-directed attacks on bacteria.) Binding of a complement protein to an antigen-antibody complex on a foreign cell (or an enveloped virus) triggers a cascade in which each protein of the complement system activates the next protein. Ultimately, activated complement proteins generate a *membrane attack complex* that forms a pore in the membrane of the foreign cell. Ions and water rush into the cell, causing it to swell and lyse (**Figure 43.19**, right).Whether activated as part of innate defenses or as part of adaptive defenses, this cascade of complement protein activity results in the lysis of foreign cells and produces factors that promote inflammation or stimulate phagocytosis.

When antibodies facilitate phagocytosis (see Figure 43.19, middle), they also help fine-tune the humoral immune response. Recall that phagocytosis enables macrophages and dendritic cells to present antigens to and stimulate helper T cells, which in turn stimulate the very B cells whose antibodies contribute to phagocytosis. This positive feedback between innate and adaptive immunity contributes to a coordinated, effective response to infection.

Although antibodies are the cornerstone of the response in body fluids, there is also a mechanism by which they can bring about the death of infected body cells. When a virus uses a cell's biosynthetic machinery to produce viral proteins, these viral products can appear on the cell surface. If antibodies specific for epitopes on these viral proteins bind to the exposed proteins, the presence of bound antibody at the cell surface can recruit a natural killer cell. The natural killer cell then releases proteins that cause the infected cell to undergo apoptosis.

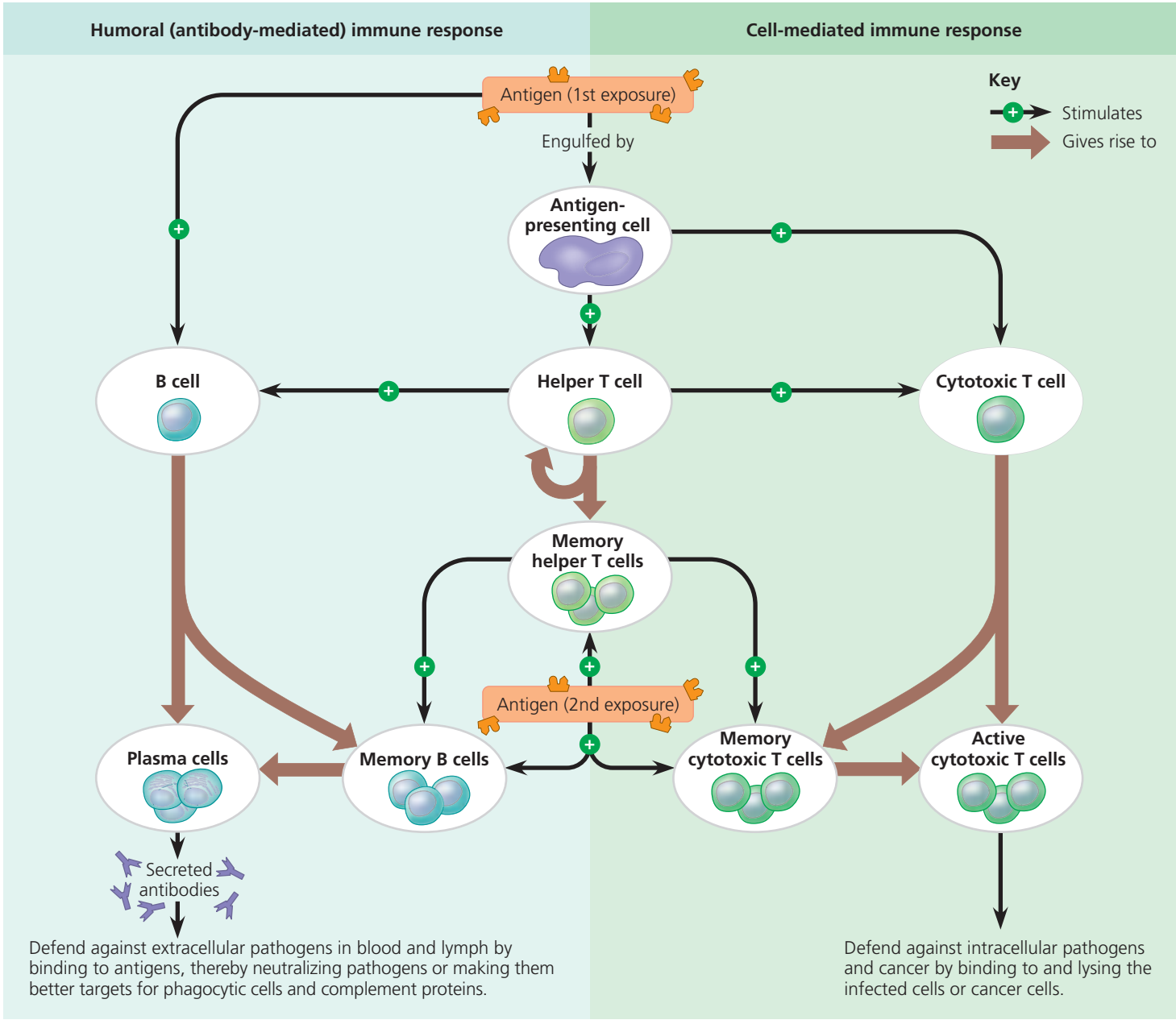
B cells can express five different forms of immunoglobulin (Ig). For a given B cell, each form or *class* has an identical antigen-binding specificity, but a distinct heavy-chain C region. The B cell antigen receptor, known as IgD, is membrane bound. The other four classes consist of soluble antibodies. IgM is the first class of soluble antibody produced. IgG, which follows next, is the most abundant antibody in blood. We will learn more about the function of IgG, as well as the two remaining antibody classes (IgA and IgE), as we further explore the role of antibodies in immunity and disease.

Summary of the Humoral and Cell-Mediated Immune Responses

As noted earlier, both the humoral and cell-mediated responses can include primary and secondary immune responses. Memory cells of each type—helper T cell, B cell, and cytotoxic T cell—enable the secondary response. For example, when body fluids are reinfected by a pathogen encountered previously, memory B cells and memory helper T cells initiate a secondary humoral response. **Figure 43.20** reviews the events that initiate humoral and cell-mediated immune responses, highlights the central role of the helper T cell, and serves as a helpful summary of adaptive immunity.

Active and Passive Immunization

Our discussion of adaptive immunity has to this point focused on **active immunity**, the defenses that arise when a pathogen infects the body and prompts a primary or secondary immune response. In contrast, a different type of immunity results when the IgG antibodies in the blood of a pregnant female cross the placenta to her fetus. The transferred antibodies can immediately react with any pathogens for which they are specific. This protection is called **passive immunity** because the antibodies provided by the mother guard against pathogens that have never infected the newborn. Because passive immunity does not involve the recipient's



▲ **Figure 43.20 An overview of the adaptive immune response.**

? *Identify each black or brown arrow as representing part of the primary or secondary response.*

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B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months).

After giving birth, a nursing mother continues to transfer protection against disease to her infant. IgA antibodies present in breast milk provide additional passive immunity to the infant's digestive tract while the infant's immune system develops. Later in life, IgA functions in active immunity: IgA antibodies secreted in tears, saliva, and mucus protect the mucous membranes of both males and females.

Both active immunity and passive immunity can be induced artificially. Active immunity can develop from the introduction of antigens into the body through **immunization**. In 1796, Edward Jenner noted that milkmaids who had cowpox, a mild disease usually seen only in cows, did not contract smallpox, a far more dangerous disease. In the first documented immunization (or **vaccination**, from the Latin *vacca,* cow), Jenner used the cowpox virus to induce adaptive immunity against the closely related smallpox virus. Today, many sources of antigen are used to make vaccines, including inactivated bacterial toxins, killed pathogens, parts of pathogens, weakened pathogens that generally do not cause illness, and even genes encoding microbial proteins. Because all of these agents induce a primary immune response and immunological memory, an encounter with the pathogen from which the vaccine was derived triggers a rapid and strong secondary immune response (see Figure 43.15).

Vaccination programs have been successful against many infectious diseases that once killed or incapacitated large numbers of people. A worldwide vaccination campaign led to eradication of smallpox in the late 1970s. In industrialized nations, routine active immunization of infants and children has dramatically reduced the incidence of sometimes devastating diseases, such as polio, measles, and whooping cough. Unfortunately, not all pathogens are easily managed by vaccination. Furthermore, some vaccines are not readily available in impoverished areas of the globe.

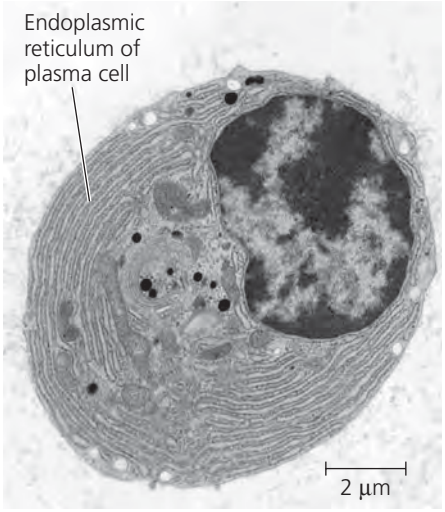
Misinformation about vaccine safety and disease risk has led some parents to refuse to immunize their children with available, effective vaccines. The consequence has been a substantial and growing public health problem. Consider measles as just one example. Side effects of immunization are remarkably rare: Fewer than one in a million children suffer a significant allergic reaction to the measles vaccine. The disease, however, is quite dangerous: Roughly one out of every 1,000 patients develop *encephalitis*, an inflammation of the brain. Worldwide, measles kills more than 200,000 people each year. Sadly, declines in measles vaccination rates in parts of the United Kingdom, Russia, and the United States have recently resulted in a number of measles outbreaks and significant numbers of preventable deaths.

In artificial passive immunization, antibodies from an immune animal are injected into a nonimmune animal. For example, humans bitten by venomous snakes are sometimes treated with antivenin, serum from sheep or horses that have been immunized against the venom of one or more species of venomous snakes. When injected immediately after a snakebite, the antibodies in antivenin can neutralize toxins in the venom before the toxins do massive damage.

Antibodies as Tools

The power of antibody specificity and antigen-antibody binding has been harnessed in research, diagnosis, and therapy. Some antibody tools are *polyclonal*: They are the products of many different clones of plasma cells, each specific for a different epitope **(Figure 43.21)**. Antibodies that an animal produces after exposure to a microbial antigen are polyclonal. In contrast, other antibody tools are *monoclonal*: They are prepared from a single clone of B cells grown in culture. The **monoclonal antibodies** produced by such a culture are identical and specific for the same epitope on an antigen.

Monoclonal antibodies have provided the basis for many recent advances in medical diagnosis and treatment. For example, home pregnancy kits use monoclonal antibodies to detect human chorionic gonadotropin (hCG). Because hCG is produced as soon as an embryo implants in the uterus (see Chapter 46), the presence of this hormone in a woman's urine is a reliable indicator for a very early stage of pregnancy. In the clinic, monoclonal antibodies are being used to treat many human diseases. For this type of therapy, researchers use mouse B cell clones to identify antibodies specific for an epitope on diseased cells. Next, the mouse antibody genes are altered to code for antibodies that appear less foreign to the human adaptive immune defenses. Scientists then use the "humanized" genes to produce large amounts of antibody for injecting into patients.



▲ **Figure 43.21 A plasma cell.** A plasma cell contains abundant endoplasmic reticulum, a common feature of cells dedicated to making proteins for secretion (TEM).

Immune Rejection

Like pathogens, cells from another person can be recognized as foreign and attacked by immune defenses. For example, skin transplanted from one person to a genetically nonidentical person will look healthy for a week or so but will then be destroyed (rejected) by the recipient's immune response. Keep in mind that the body's rejection of transplanted tissues or

organs or of an incompatible blood transfusion is the expected reaction of a healthy immune system exposed to foreign antigens. (It remains a largely unanswered question why a pregnant woman does not reject her fetus as nonself tissue.)

Blood Groups

To avoid a blood transfusion being recognized as foreign by the recipient's immune system, the ABO blood groups of the donor and recipient must be taken into account. As discussed in Chapter 14, red blood cells are designated as type A if they have the type A carbohydrate on their surface. Similarly, the type B carbohydrate is found on type B red blood cells; both A and B carbohydrates are found on type AB red blood cells; and neither carbohydrate is found on type O red blood cells (see Figure 14.11).

To understand how ABO blood groups affect transfusions, let's consider the immune response of someone with type A blood. It turns out that certain bacteria normally present in the body have epitopes very similar to the A and B carbohydrates. By responding to the bacterial epitope similar to the B carbohydrate, a person with type A blood makes antibodies that will react with the type B carbohydrate. No antibodies are made against the bacterial epitope similar to the type A carbohydrate because lymphocytes reactive with the body's own molecules are inactivated or eliminated during development. If the person with type A blood receives a transfusion of type B blood, that person's anti-B antibodies cause an immediate and devastating transfusion reaction. The transfused red blood cells undergo lysis, which can lead to chills, fever, shock, and kidney malfunction. By the same token, anti-A antibodies in the donated type B blood will act against the recipient's type A red blood cells. Although such interactions prevent type O individuals from receiving transfusions of any other blood type, the recent discovery of enzymes that can cleave the A and B carbohydrates from red blood cells may eliminate this problem.

Tissue and Organ Transplants

In the case of tissue and organ transplants, or grafts, MHC molecules stimulate the immune response that leads to rejection. Each vertebrate species has many alleles for each MHC gene, enabling presentation of antigen fragments that vary in shape and net electrical charge. This diversity of MHC molecules almost guarantees that no two people, except identical twins, will have exactly the same set. Thus, in the vast majority of graft and transplant recipients, some MHC molecules on the donated tissue are foreign to the recipient. To minimize rejection, physicians use donor tissue bearing MHC molecules that match those of the recipient as closely as possible. In addition, the recipient takes medicines that suppress immune responses (but also leave the recipient more susceptible to infections).

Transplants of bone marrow from one person to another can also cause an immune reaction, but for a different reason. Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological (blood cell) diseases. Prior to receiving transplanted bone marrow, the recipient is typically treated with radiation to eliminate his or her own bone marrow cells, thus destroying the source of abnormal cells. This treatment effectively obliterates the recipient's immune system, leaving little chance of graft rejection. However, lymphocytes in the donated marrow may react against the recipient. This *graft versus host reaction* is limited if the MHC molecules of the donor and recipient are well matched. Bone marrow donor programs continually seek volunteers because the great variability of MHC molecules makes a diverse pool of donors essential.

CONCEPT CHECK 43.3

1. If a child were born without a thymus, what cells and functions would be deficient? Explain.
2. Treatment of antibodies with a particular protease clips the heavy chains in half, releasing the two arms of the Y-shaped molecule. How might the antibodies continue to function?
3. **WHAT IF?** Suppose that a snake handler bitten by a particular venomous snake species was treated with antivenin. Why might the same treatment for a second such bite have different results?

For suggested answers, see Appendix A.

CONCEPT 43.4

Disruptions in immune system function can elicit or exacerbate disease

Although adaptive immunity offers significant protection against a wide range of pathogens, it is not fail-safe. In this last section of the chapter, we'll first examine the problems that arise when adaptive immunity is blocked or misregulated. We'll then turn to some of the evolutionary adaptations of pathogens that diminish the effectiveness of host immune responses.

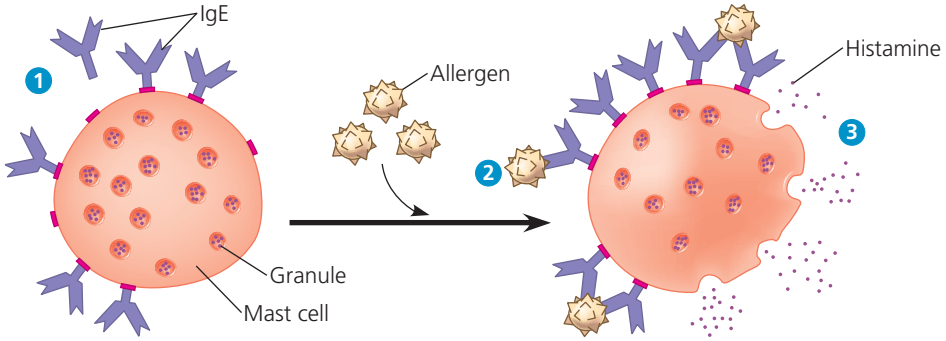
Exaggerated, Self-Directed, and Diminished Immune Responses

The highly regulated interplay among lymphocytes, other body cells, and foreign substances generates an immune response that provides extraordinary protection against many pathogens. When allergic, autoimmune, or immunodeficiency disorders disrupt this delicate balance, the effects are frequently severe and sometimes life-threatening.

Allergies

Allergies are exaggerated (hypersensitive) responses to certain antigens called **allergens**. The most common allergies involve antibodies of the IgE class. Hay fever, for instance, occurs when plasma cells secrete IgE antibodies specific for antigens on the surface of pollen grains **(Figure 43.22)**. Some IgE antibodies attach by their base to mast cells in connective tissues. Pollen grains that enter the body later attach to the antigen-binding sites of these IgE antibodies. This attachment links adjacent IgE molecules, inducing the mast cell to release histamine and other inflammatory chemicals from granules (vesicles). Acting on a variety of cell types, these signals bring about the typical allergy symptoms: sneezing, runny nose, teary eyes, and smooth muscle contractions that can result in breathing difficulty. Drugs called antihistamines diminish allergy symptoms (and inflammation) by blocking receptors for histamine.

An acute allergic response sometimes leads to *anaphylactic shock*, a whole-body, life-threatening reaction that can occur within seconds of exposure to an allergen. Anaphylactic shock develops when widespread release of mast cell contents triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure, as well as constriction of bronchioles. Death may occur within minutes due to lack of blood flow and the inability to breathe. Allergic responses to bee venom or penicillin can lead to anaphylactic shock in people who are extremely allergic to these substances. Likewise, people very allergic to peanuts, fish, or shellfish can die from ingesting only tiny amounts of these allergens, which trigger reactions through interactions with mast cells on the surface of the digestive tract. People with severe hypersensitivities often carry syringes containing the hormone epinephrine, which counteracts this allergic response (see Figure 45.8).



1 IgE antibodies produced in response to initial exposure to an allergen bind to receptors on mast cells.

2 On subsequent exposure to the same allergen, IgE molecules attached to a mast cell recognize and bind the allergen.

3 Cross-linking of adjacent IgE molecules triggers release of histamine and other chemicals, leading to allergy symptoms.

▲ **Figure 43.22 Mast cells, IgE, and the allergic response.** In this example, pollen grains act as the allergen.

Autoimmune Diseases

In some people, the immune system is active against particular molecules of the body, causing an **autoimmune disease**. Such a loss of self-tolerance has many forms. In *systemic lupus erythematosus*, commonly called *lupus*, the immune system generates antibodies against histones and DNA released by the normal breakdown of body cells. These self-reactive antibodies cause skin rashes, fever, arthritis, and kidney dysfunction. Another autoimmune disease, *rheumatoid arthritis*, leads to damage and painful inflammation of the cartilage and bone of joints **(Figure 43.23)**. In *type 1 diabetes mellitus*, the insulin-producing beta cells of the pancreas are the targets of autoimmune cytotoxic T cells. The most common chronic neurological disorder in developed countries is the autoimmune disease *multiple sclerosis*. In this disease, T cells infiltrate the central nervous system. The result is destruction of the myelin sheath that surrounds parts of many neurons (see Figure 48.12), leading to muscle paralysis through a disruption in neuron function.

▲ **Figure 43.23 X-ray of hands deformed by rheumatoid arthritis.**

Gender, genetics, and environment all influence susceptibility to autoimmune disorders. For example, members of certain families show an increased susceptibility to particular autoimmune disorders. In addition, many autoimmune diseases afflict females more often than males. Women are two to three times more likely than men to suffer from multiple sclerosis and rheumatoid arthritis and nine times more likely to develop lupus. The cause of this sex bias, as well as the rise in autoimmune disease frequency in industrialized countries, is an area of active research and debate. Clearly, much remains to be learned about these often devastating disorders.

Exertion, Stress, and the Immune System

Many forms of exertion and stress influence immune system function. Consider, for example, susceptibility to the common cold and other infections of the upper respiratory tract. Moderate exercise improves immune system function and significantly reduces the risk of these infections. In contrast,

exercise to the point of exhaustion leads to more frequent infections and to more severe symptoms. Studies of marathon runners support the conclusion that exercise intensity is the critical variable. On average, such runners get sick less often than their more sedentary peers during training, a time of moderate exertion, but have a marked increase in illness in the period immediately following the grueling race itself. Similarly, psychological stress has been shown to disrupt immune system regulation by altering the interplay of the hormonal, nervous, and immune systems (see Figure 45.21). Recent research also confirms that rest is important for immunity: Adults who averaged fewer than 7 hours of sleep a night got sick three times as often when exposed to a cold virus as individuals who averaged at least 8 hours of sleep.

Immunodeficiency Diseases

A disorder in which an immune system response to antigens is defective or absent is called an **immunodeficiency**. An *inborn immunodeficiency* results from a genetic or developmental defect in the immune system. An *acquired immunodeficiency* develops later in life following exposure to chemical or biological agents. Whatever its cause and nature, an immunodeficiency can lead to frequent and recurrent infections and increased susceptibility to certain cancers.

Inborn immunodeficiencies result from defects in the development of various immune system cells or defects in the production of specific proteins, such as antibodies or the proteins of the complement system. Depending on the specific genetic defect, either innate or adaptive defenses—or both—may be impaired. In severe combined immunodeficiency (SCID), functional lymphocytes are rare or absent. Lacking an adaptive immune response, SCID patients are susceptible to infections, such as pneumonia and meningitis, that can cause death in infancy. Treatments include bone marrow and stem cell transplantation.

Exposure to certain agents can cause immunodeficiencies that develop later in life. Drugs used to fight autoimmune diseases or prevent transplant rejection suppress the immune system, leading to an immunodeficient state. Certain cancers also suppress the immune system, especially Hodgkin's disease, which damages the lymphatic system. Acquired immunodeficiencies range from temporary states that may arise from physiological stress to the devastating **acquired immunodeficiency syndrome (AIDS)**, which is caused by the human immunodeficiency virus (HIV). We will discuss AIDS further in the next section, which focuses on how pathogens escape the adaptive immune response.

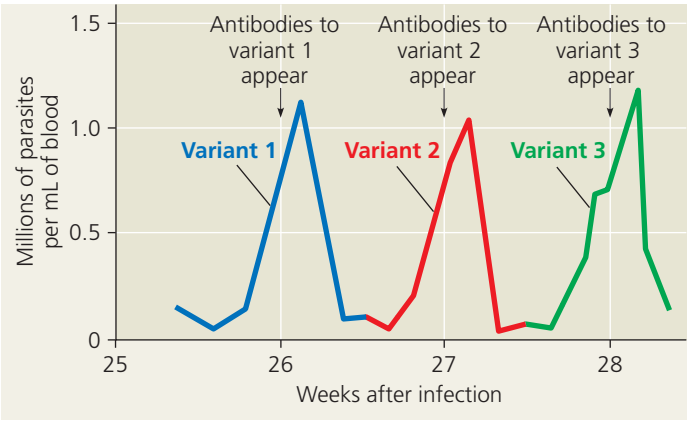
Evolutionary Adaptations of Pathogens That Underlie Immune System Avoidance

EVOLUTION Just as immune systems that ward off pathogens have evolved in animals, mechanisms that thwart immune responses have evolved in pathogens. Using human pathogens as examples, we'll examine some common mechanisms: antigenic variation, latency, and direct attack on the immune system.

Antigenic Variation

One mechanism for escaping the body's defenses is for a pathogen to alter how it appears to the immune system. Immunological memory is a record of the foreign epitopes an animal has encountered. If the pathogen that expressed those epitopes no longer does so, it can reinfect or remain in a host without triggering the rapid and robust response that memory cells provide. Such changes in epitope expression, which are called *antigenic variation*, are regular events for some viruses and parasites. The parasite that causes sleeping sickness (trypanosomiasis) provides one example. By periodically switching at random among 1,000 different versions of the protein found over its entire surface, this pathogen can persist in the body without facing an effective adaptive immune response **(Figure 43.24)**.

Antigenic variation is the major reason the influenza, or "flu," virus remains a major public health problem. As it replicates in one human host after another, the human influenza virus mutates. Because any change that lessens recognition by the immune system provides a selective advantage, the virus steadily accumulates such alterations. These changes in the surface proteins of the influenza virus are the reason that a new flu vaccine must be manufactured and distributed each year. Of much greater danger, however, is the fact that the human virus occasionally exchanges genes with influenza viruses that infect domesticated animals, such as pigs or chickens. When this occurs, influenza can take on such a radically different appearance that none of the memory cells in



▲ **Figure 43.24 Antigenic variation in the parasite that causes sleeping sickness.** Blood samples taken from a patient during a chronic infection of sleeping sickness reveal cyclic variation in the surface coat protein of the parasite. The infection has become chronic because this weekly variation allows the parasite to evade the adaptive immune response.

the human population recognize the new strain. Such an event led to the influenza outbreak of 1918–1919, which killed more than half a million people in the United States (see Figure 19.9). Worldwide more than 20 million people died, a greater number than had died in World War I.

In 2009, an influenza virus called H1N1 appeared that contained a novel combination of genes from flu viruses that normally circulate in pigs, birds, and humans. The rapid spread of this flu across the human population caused a *pandemic*, an outbreak of worldwide proportions. Fortunately, a rapidly developed H1N1 vaccine soon provided public health officials with an excellent means of slowing the spread of this virus and reducing the impact of the outbreak.

Latency

After infecting a host, some viruses enter a largely inactive state called *latency*. Because such dormant viruses cease making most viral proteins and typically produce no free virus particles, they do not trigger an adaptive immune response. Nevertheless, the viral genome persists in the nuclei of infected cells, either as a separate small DNA molecule or as a copy integrated into the host genome. Latency typically persists until conditions arise that are favorable for viral transmission or unfavorable for host survival, such as when the host is infected by another pathogen. Such circumstances trigger the synthesis and release of virus particles that can infect new hosts.

Herpes simplex viruses, which establish themselves in human sensory neurons, provide a good example of latency. The type 1 virus causes most oral herpes infections, whereas the type 2 virus is responsible for most cases of genital herpes. Because sensory neurons express relatively few MHC I molecules, the infected cells are inefficient at presenting viral antigens to circulating lymphocytes. Stimuli such as fever, emotional stress, or menstruation reactivate the virus to reproduce and infect surrounding epithelial tissues. Activation of the type 1 virus can result in blisters around the mouth that are inaccurately called "cold" sores. The type 2 virus can cause genital sores, but people infected with either type 1 or type 2 virus often lack any apparent symptoms. Infections of the type 2 virus, which is sexually transmitted, pose a serious threat to the babies of infected mothers and can increase transmission of HIV, the virus that causes AIDS.

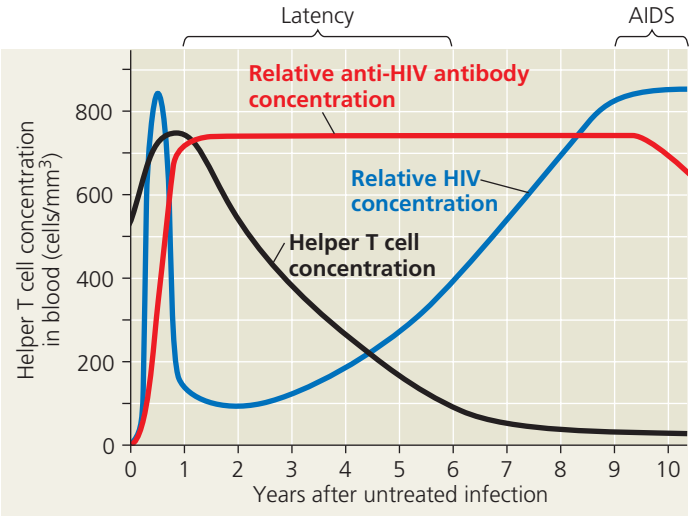
Attack on the Immune System: HIV

The human immunodeficiency virus (HIV), the pathogen that causes AIDS, both escapes and attacks the adaptive immune response. Once introduced into the body, HIV infects helper T cells with high efficiency. To infect these cells, the virus binds specifically to the CD4 accessory protein (see Figure 43.16). However, HIV also infects some cell types that have low levels of CD4, such as macrophages and brain cells. In the cell, the HIV RNA genome is reverse-transcribed, and the product DNA is integrated into the host cell's genome (see Figure 19.8). In this form, the viral genome can direct production of new virus particles.

Although the body responds to HIV with an immune response sufficient to eliminate most viral infections, some HIV invariably escapes. One reason HIV persists is antigenic variation. The virus mutates at a very high rate during replication. Altered proteins on the surface of some mutated viruses reduce interaction with antibodies and cytotoxic T cells. Such viruses survive, proliferate, and mutate further. The virus thus evolves within the body. The continued presence of HIV is also helped by latency. When the viral DNA integrates into the chromosome of a host cell but does not produce new virus proteins or particles, it is shielded from the immune system by the host cell. This inactive, or latent, viral DNA is also protected from antiviral agents currently used against HIV because they attack only actively replicating viruses.

Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it **(Figure 43.25)**. Viral reproduction and cell death triggered by the virus lead to loss of helper T cells, impairing both humoral and cell-mediated immune responses. The result is a progression to AIDS, characterized by a susceptibility to infections and cancers that a healthy immune system would usually defeat. For example, *Pneumocystis carinii*, a common fungus that does not cause disease in healthy individuals, can result in severe pneumonia in people with AIDS. Likewise, the Kaposi's sarcoma herpesvirus causes a cancer among AIDS patients that is extremely rare in individuals not infected with HIV. Such opportunistic diseases, as well as nerve damage and body wasting, are the primary causes of death in AIDS patients, not the HIV virus itself.

At present, HIV infection cannot be cured, although certain drugs can slow HIV reproduction and the progression to



▲ Figure 43.25 The progress of an untreated HIV infection.

AIDS. Unfortunately, mutations that occur in each round of viral reproduction can generate strains of HIV that are drug resistant. The impact of such viral drug resistance can be reduced by the use of a combination of drugs; viruses newly resistant to one drug can be defeated by another. However, the appearance of strains resistant to multiple drugs reduces the effectiveness of such multidrug "cocktails" in some patients. Frequent mutations in genes for HIV surface antigens also have hampered efforts to develop an effective vaccine. Worldwide, the AIDS epidemic continues to grow. In 2008, approximately 2 million people died of AIDS, and the disease is now the leading cause of death in Africa.

Transmission of HIV requires the transfer of virus particles or infected cells from person to person via body fluids such as semen, blood, or breast milk. Unprotected sex (that is, without a condom) and transmission via HIV-contaminated needles (typically among intravenous drug users) account for the vast majority of HIV infections. The virus can enter the body through the mucosal linings of the vagina, vulva, penis, or rectum during intercourse or via the mouth during oral sex. The likelihood of transmission is increased by factors that may damage these linings, especially other sexually transmitted infections that cause ulcers or inflammation.

People infected with HIV can transmit the disease in the first few weeks of infection, *before* they express HIV-specific antibodies that can be detected in a blood test (see Figure 43.25). Currently, 10–50% of all new HIV infections appear to be caused by recently infected individuals.

Cancer and Immunity

When adaptive immunity is inactivated, the frequency of certain cancers increases dramatically. For example, the risk of developing Kaposi's sarcoma is 20,000 times greater for untreated AIDS patients than for healthy people. This observation was unanticipated. If the immune system recognizes only nonself, it should fail to recognize the uncontrolled growth of self cells that is the hallmark of cancer. It turns out, however, that viruses are involved in about 15–20% of all human cancers. Because the immune system can recognize viral proteins as foreign, it can act as a defense against viruses that can cause cancer and against cancer cells that harbor viruses.

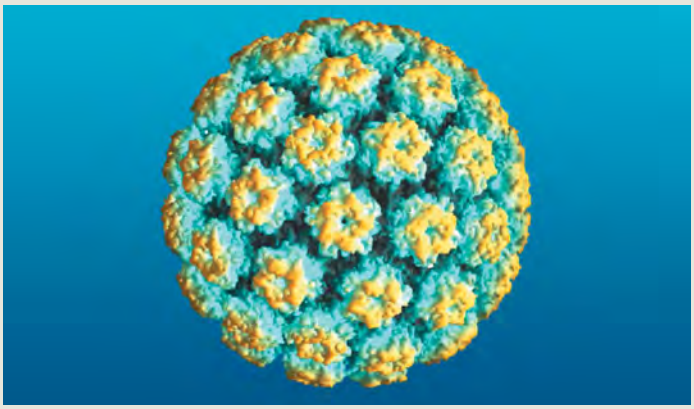
Scientists have identified six viruses that can cause cancer in humans. The Kaposi's sarcoma herpesvirus is one such virus. Hepatitis B virus, which can trigger liver cancer, is another. A vaccine directed against hepatitis B virus that was introduced in 1986 was demonstrated to be the first vaccine to help prevent a specific human cancer. Rapid progress on virus-induced cancers continues. In 2006, the release of a vaccine against cervical cancer, specifically human papillomavirus (HPV), marked a major victory against a disease that afflicts more than half a million women worldwide every year **(Figure 43.26)**.

▼ **Figure 43.26**

IMPACT

Vaccinating Against Cervical Cancer

In the 1970s, Harald zur Hausen, working in Heidelberg, Germany, proposed that human papillomavirus (HPV) causes cervical cancer. Many scientists were skeptical that cancer could result from infection by HPV, the most common sexually transmitted pathogen. However, after more than a decade of work, zur Hausen isolated two particular types of HPV from patients with cervical cancer. He quickly made samples available to other scientists, leading to development of highly effective vaccines against cervical cancer. In 2008, zur Hausen shared the Nobel Prize in Physiology or Medicine for his discovery. This computer graphic image of an HPV particle illustrates the abundant copies of the capsid protein (yellow) that is used as the antigen in vaccination.



WHY IT MATTERS Cervical cancer kills more than 4,000 women annually in the United States and is the fifth-most common cause of cancer deaths among women worldwide. Administering an HPV vaccine, either Gardasil or Cervarix, to preteen girls and young women greatly reduces their chance of being infected with the HPV viruses that cause most cervical cancers.

FURTHER READING L. R. Badenet et al., Human papillomavirus vaccine: Opportunity and challenge, *New England Journal of Medicine* 356:1990–1991 (2007).

WHAT IF? Suppose you tracked the health of women infected with the types of HPV that cause cancer. Why might only a fraction of such women develop cervical cancer? (*Hint*: Refer to Figure 18.25 on p. 376 and the accompanying text.)

CONCEPT CHECK 43.4

1. In myasthenia gravis, antibodies bind to and block certain receptors on muscle cells, preventing muscle contraction. Is this disease best classified as an immunodeficiency disease, an autoimmune disease, or an allergic reaction? Explain.
2. People with herpes simplex type 1 viruses often get mouth sores when they have a cold or similar infection. How might this location benefit the virus?
3. **WHAT IF?** How would a macrophage deficiency likely affect a person's innate and adaptive defenses?

For suggested answers, see Appendix A.

43 CHAPTER REVIEW

SUMMARY OF KEY CONCEPTS

CONCEPT 43.1

In innate immunity, recognition and response rely on traits common to groups of pathogens (pp. 930–935)

- In both invertebrates and vertebrates, **innate immunity** is mediated by physical and chemical barriers as well as cell-based defenses. Activation of innate immune responses relies on recognition proteins specific for broad classes of **pathogens**. In insects, pathogens that penetrate barrier defenses are ingested by cells in the hemolymph that also release antimicrobial peptides.
- In vertebrates, intact skin and mucous membranes form barriers to pathogens. Mucus produced by membrane cells, the low pH of the skin and stomach, and degradation by **lysozyme** also deter pathogens. Microbes that penetrate barrier defenses are ingested by phagocytic cells, including **macrophages** and **dendritic cells**. Additional cellular defenses include **natural killer cells**, which can induce the death of virus-infected cells. **Complement system** proteins, **interferons**, and other antimicrobial peptides also act against microbes. In the **inflammatory response**, **histamine** and other chemicals released from cells at the injury site promote changes in blood vessels that allow fluid, more phagocytic cells, and antimicrobial peptides to enter tissues.
- Pathogens sometimes evade innate immune defenses. For example, some bacteria have an outer capsule that prevents recognition, while others are resistant to breakdown within lysosomes.

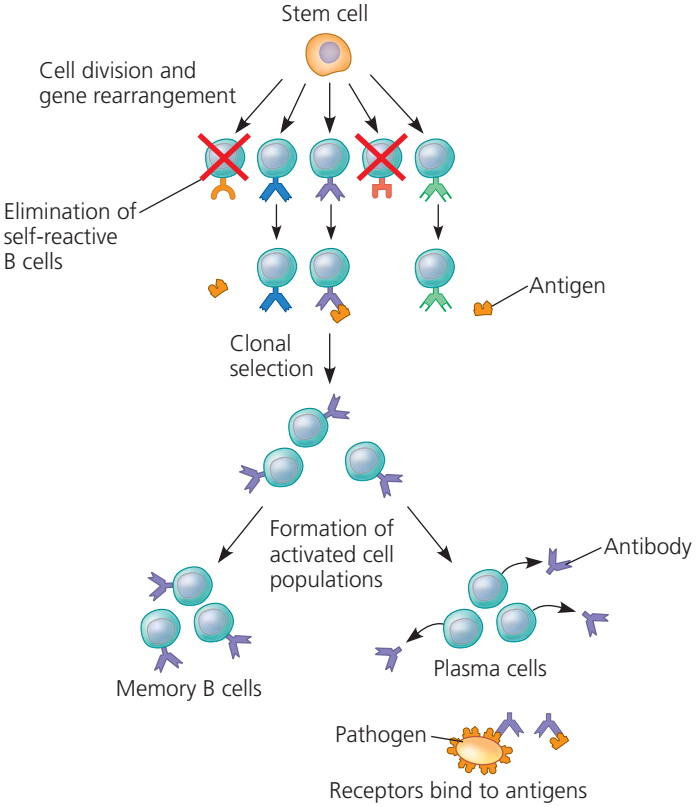
? *In what ways does innate immunity protect the mammalian digestive tract?*

CONCEPT 43.2

In adaptive immunity, receptors provide pathogen-specific recognition (pp. 935–940)

- **Adaptive immunity** relies on **lymphocytes** that arise from stem cells in the bone marrow and complete their maturation in the bone marrow (**B cells**) or in the **thymus** (**T cells**). Lymphocytes have cell-surface **antigen receptors** for foreign molecules. All receptor proteins on a single B or T cell are the same, but there are millions of B and T cells in the body that differ in the foreign molecules that their receptors recognize. Upon infection, B and T cells specific for the pathogen are activated. Some T cells help other lymphocytes; others kill infected host cells. B cells called **plasma cells** produce soluble receptor proteins called **antibodies**, which bind to foreign molecules and cells. The activated lymphocytes called **memory cells** defend against future infections by the same pathogen.
- Recognition of foreign molecules involves the binding of variable regions of receptors to an **epitope**, a small region of an antigen. B cells and antibodies recognize epitopes on the surface of antigens circulating in the blood or lymph. T cells recognize protein epitopes in small antigen fragments (peptides) that are presented on the surface of host cells, complexed with cell-surface proteins called **MHC (major histocompatibility complex) molecules**.
- The four major characteristics of B and T cell development are the generation of cell diversity, self-tolerance, proliferation, and immunological memory.

The following figure uses B cells to illustrate clonal selection:



? *Why is the adaptive immune response to an initial infection slower than the innate response?*

CONCEPT 43.3

Adaptive immunity defends against infection of body fluids and body cells (pp. 940–946)

- **Helper T cells** interact with antigen fragments displayed by class II MHC molecules on the surface of dendritic cells, macrophages, and B cells (**antigen-presenting cells**). Activated helper T cells secrete **cytokines** that stimulate other lymphocytes as part of the response to nearly all antigens. **Cytotoxic T cells** bind to a complex of an antigen fragment and a class I MHC molecule on infected host cells. In the **cell-mediated immune response**, activated cytotoxic T cells secrete proteins that initiate destruction of infected cells. All T cells have an accessory protein that enhances binding to MHC–antigen fragment complexes.

  In the **humoral immune response**, B cell antigen receptors and antibodies bind to extracellular foreign substances in blood and lymph.The binding of antibodies helps eliminate antigens by phagocytosis and complement-mediated lysis. The five major antibody classes differ in distribution and function.
- **Active immunity** develops in response to infection or to immunization with a nonpathogenic form or part of a pathogen. Active immunity includes a response to and immunological memory for that pathogen. **Passive immunity**, which provides immediate, short-term protection, is conferred naturally when IgG crosses the placenta from mother to fetus or when IgA passes from mother to infant in breast milk. It also can be conferred artificially by injecting antibodies into a nonimmune person.

- Tissues or cells transferred from one person to another are subject to immune rejection. In tissue grafts and organ transplants, MHC molecules stimulate rejection. Lymphocytes in bone marrow transplants may cause a graft versus host reaction.

? *Is immunological memory after a natural infection fundamentally different from immunological memory after vaccination? Explain.*

CONCEPT 43.4

Disruptions in immune system function can elicit or exacerbate disease (pp. 946–950)

- Disruption of normal immune system regulation or function can result in an exaggerated, self-directed, or diminished response. In localized allergies, IgE attached to **mast cells** induces the cells to release histamine and other mediators that cause vascular changes and allergic symptoms. Loss of self-tolerance can lead to **autoimmune diseases**, such as multiple sclerosis. Inborn **immunodeficiencies** result from defects that interfere with innate, humoral, or cell-mediated defenses. **AIDS** is an acquired immunodeficiency caused by HIV.
- Antigenic variation, latency, and direct assault on the immune system allow some pathogens to thwart immune responses. HIV infection destroys helper T cells, leaving the patient prone to disease. Immune defense against cancer appears to primarily involve action against viruses that can cause cancer, as well as against cancer cells that harbor viruses.

? *Is being infected with HIV the same as having AIDS? Explain.*

TEST YOUR UNDERSTANDING

LEVEL 1: KNOWLEDGE/COMPREHENSION

1. Which of these is *not* part of insect immunity?
   a. enzyme activation of microbe-killing chemicals
   b. activation of natural killer cells
   c. phagocytosis by hemocytes
   d. production of antimicrobial peptides
   e. a protective exoskeleton
2. An epitope associates with which part of an antigen receptor or antibody?
   a. the disulfide bridge
   b. the heavy-chain constant regions only
   c. variable regions of a heavy chain and light chain combined
   d. the light-chain constant regions only
   e. the tail
3. Which statement best describes the difference in responses of effector B cells (plasma cells) and cytotoxic T cells?
   a. B cells confer active immunity; cytotoxic T cells confer passive immunity.
   b. B cells kill pathogens directly; cytotoxic T cells kill host cells.
   c. B cells secrete antibodies against a pathogen; cytotoxic T cells kill pathogen-infected host cells.
   d. B cells carry out the cell-mediated response; cytotoxic T cells carry out the humoral response.
   e. B cells respond the first time a pathogen is present; cytotoxic T cells respond subsequent times.

LEVEL 2: APPLICATION/ANALYSIS

4. Which of the following statements is *not* true?
   a. An antibody has more than one antigen-binding site.
   b. An antigen can have different epitopes.
   c. A pathogen makes more than one antigen.
   d. A lymphocyte has receptors for multiple different antigens.
   e. A liver cell makes one class of MHC molecule.
5. Which of the following should be the same in identical twins?
   a. the set of antibodies produced
   b. the set of MHC molecules produced
   c. the set of T cell antigen receptors produced
   d. the susceptibility to a particular virus
   e. the set of immune cells eliminated as self-reactive

LEVEL 3: SYNTHESIS/EVALUATION

6. Vaccination increases the number of
   a. different receptors that recognize a pathogen.
   b. lymphocytes with receptors that can bind to the pathogen.
   c. epitopes that the immune system can recognize.
   d. macrophages specific for a pathogen.
   e. MHC molecules that can present an antigen.
7. Which of the following would *not* help a virus avoid triggering an adaptive immune response?
   a. having frequent mutations in genes for surface proteins
   b. infecting cells that produce very few MHC molecules
   c. producing proteins very similar to those of other viruses
   d. infecting and killing helper T cells
   e. building the viral shell from host proteins
8. **DRAW IT** Consider a pencil-shaped protein with two epitopes, Y (the "eraser" end) and Z (the "point" end). They are recognized by antibodies A1 and A2, respectively. Draw and label a picture showing the antibodies linking proteins into a complex that could trigger endocytosis by a macrophage.
9. **MAKE CONNECTIONS** Contrast Lamarck's idea for the inheritance of acquired characteristics, discussed on pp. 454–455 of Concept 22.1, with the clonal selection of lymphocytes.
10. **EVOLUTION CONNECTION** Describe one invertebrate defense mechanism and discuss how it is an evolutionary adaptation retained in vertebrates.
11. **SCIENTIFIC INQUIRY** A diagnostic test for tuberculosis (TB) involves injecting antigen (from the bacterium that causes TB) under the skin and then waiting a few days for a reaction to appear. This test is *not* useful for diagnosing TB in AIDS patients. Why?
12. **WRITE ABOUT A THEME**

    The Genetic Basis of Life Among all nucleated body cells, only B and T cells lose DNA during their development and maturation. In a short essay (100–150 words), discuss the relationship between this loss and the theme of DNA as heritable biological information, focusing on similarities between cellular and organismal generations.

For selected answers, see Appendix A.

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1. MasteringBiology® Assignments

Tutorial Acquired Immunity
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Questions Student Misconceptions • Reading Quiz • Multiple Choice • End-of-Chapter

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