

antimicrobial peptide in the fly's body can provide an effective and specific immune defense against a particular pathogen.

## Innate Immunity of Vertebrates

In vertebrates, innate immune defenses coexist with the more recently evolved system of acquired immunity. We'll focus here on mammals because most of the recent discoveries regarding vertebrate innate immunity have come from studies of mice and humans. First we'll outline the innate defenses that are similar to those found among invertebrates: barrier defenses, phagocytosis, and antimicrobial peptides. Then we'll examine two unique aspects of vertebrate innate immunity: the inflammatory response and natural killer cells.

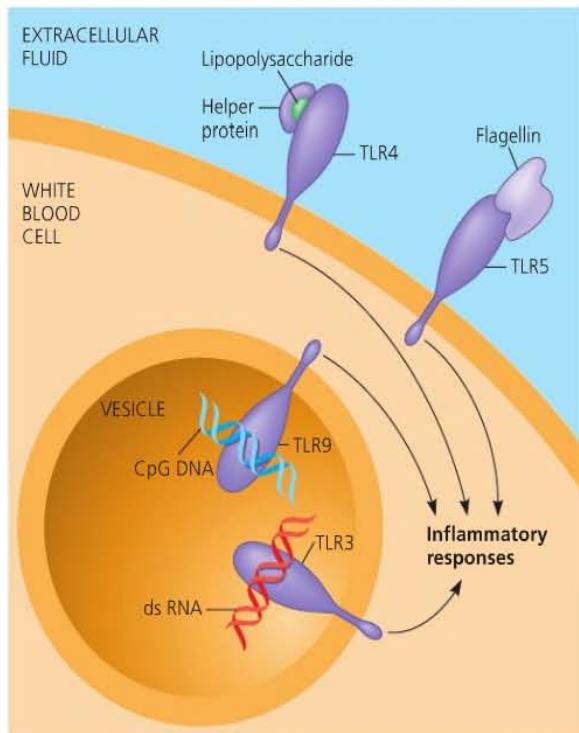
### Barrier Defenses

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 the various exposed epithelia provide a washing action that also inhibits colonization by microbes.

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

### Cellular Innate Defenses

Pathogens that make their way into the body are subject to detection by phagocytic white blood cells (leukocytes). These cells recognize microbes using receptors that are very similar to the Toll receptor of insects. Each mammalian **Toll-like receptor**, or TLR, recognizes fragments of molecules characteristic of a set of pathogens (**Figure 43.6**). For example, TLR4, located on immune cell plasma membranes, recognizes lipopolysaccharide, a type of molecule found on the surface of many bacteria. Similarly, 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. In each case, the recognized macromol-



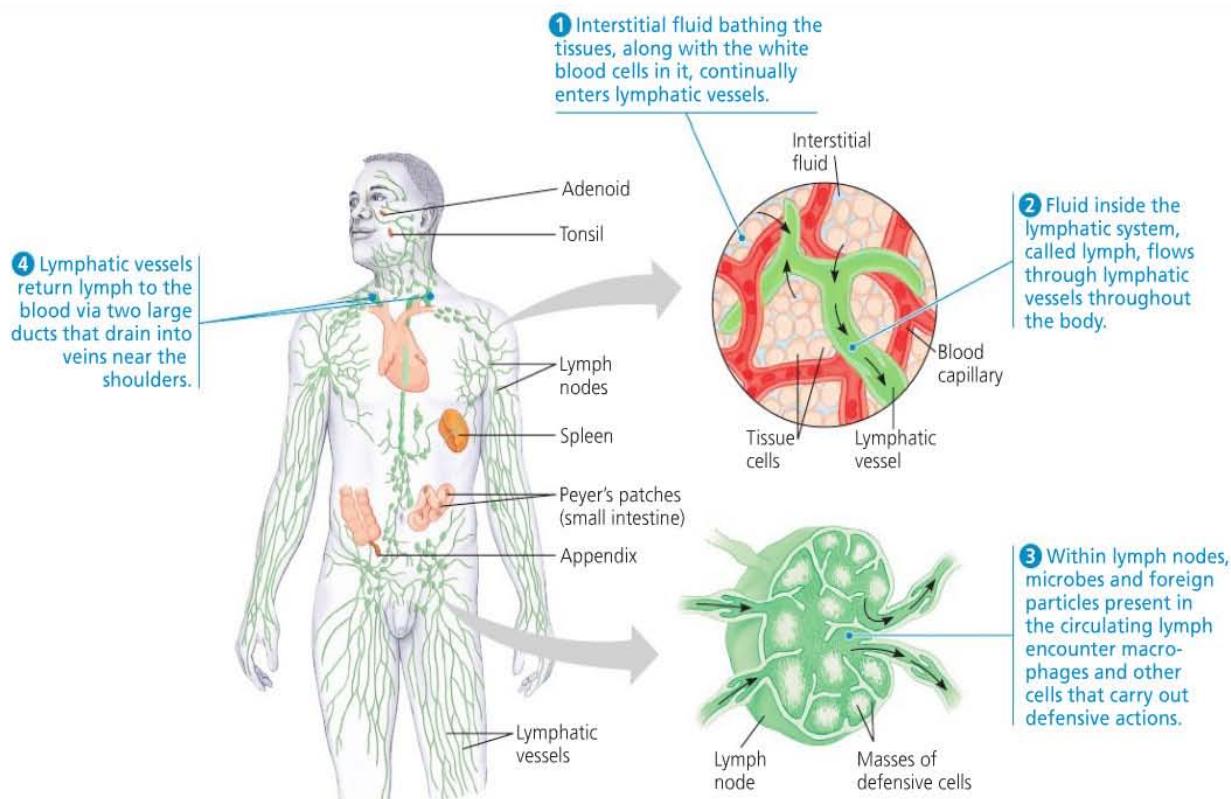
▲ **Figure 43.6 TLR signaling.** Each human Toll-like receptor (TLR) recognizes a molecular pattern characteristic of a group of pathogens. Lipopolysaccharide, flagellin, CpG DNA (DNA containing unmethylated CG sequences), and double-stranded (ds) RNA are all found in microorganisms or viruses, but not 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.

ecule is normally absent from the vertebrate body and is an essential component of a class of microbes.

As in insects, recognition by a TLR triggers a series of internal defenses, beginning with phagocytosis. A white blood cell recognizes and engulfs invading microbes, trapping them in a vacuole. The vacuole then fuses with a lysosome (see Figure 43.3), leading to destruction of the microbes in two ways. First, nitric oxide and other gases produced in the lysosome poison the engulfed microbes. Second, lysozyme and other enzymes degrade microbial components.

The most abundant phagocytic cells in the mammalian body are **neutrophils** (see Figure 42.17). Signals from infected tissues attract neutrophils, which then engulf and destroy microbes. **Macrophages** ("big eaters"), like the one shown in Figure 43.1, provide an even more effective phagocytic defense. Some of these large phagocytic cells migrate throughout the body, while others reside permanently in various organs and tissues. Macrophages in the spleen, lymph nodes, and other tissues of the lymphatic system are particularly well positioned to combat pathogens. Microbes in the blood become trapped in the spleen,



**▲ Figure 43.7 The human lymphatic system.** The lymphatic system consists of lymphatic vessels, through which lymph travels, and various structures that trap “foreign” molecules and particles. These structures include the adenoids, tonsils, lymph nodes, spleen, Peyer’s patches, and appendix. Steps 1–4 trace the flow of lymph.

whereas microbes in interstitial fluid flow into lymph and are trapped in lymph nodes. In either location, they encounter resident macrophages. **Figure 43.7** provides an overview of the lymphatic system and its role in the body’s defenses.

Two other types of phagocytes—eosinophils and dendritic cells—play more limited roles in innate defense. **Eosinophils** have low phagocytic activity but are important in defending against multicellular invaders, such as parasitic worms. Rather than engulfing such parasites, eosinophils position themselves against the parasite’s body and then discharge destructive enzymes that damage the invader. **Dendritic cells** populate tissues that are in contact with the environment. They mainly stimulate development of acquired immunity against microbes they encounter, a function we will explore later in this chapter.

#### Antimicrobial Peptides and Proteins

Pathogen recognition in mammals triggers the production and release of a variety of peptides and proteins that attack microbes 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 against viral infections. Virus-infected body cells secrete interferons, inducing 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 mass-produce interferons by recombinant DNA technology for treating certain viral infections, such as hepatitis C.

The **complement system** consists of roughly 30 proteins in blood plasma that function together to fight infections. 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 leading to lysis (bursting) of invading cells. The complement system also functions in inflammation, our next topic, as well as in the acquired defenses discussed later in the chapter.

## Inflammatory Responses

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. One important inflammatory signaling molecule is **histamine**, which is stored in **mast cells**, connective tissue cells that store chemicals in granules for secretion. **Figure 43.8** summarizes the progression of events in local inflammation, starting with infection from a splinter. Histamine released by mast cells at sites of tissue damage triggers nearby blood vessels to dilate and become more permeable. Activated macrophages and other cells discharge additional signaling molecules that further promote blood flow to the injured site. The resulting increase in local blood supply causes the redness and heat typical of inflammation (from the Latin *inflammare*, to set on fire). Capillaries engorged with blood leak fluid into neighboring tissues, causing swelling.

During inflammation, cycles of signaling and response transform the infection site. Enhanced blood flow to the injury site helps deliver antimicrobial proteins. Activated complement proteins promote further release of histamine and help attract phagocytes. Nearby endothelial cells secrete signaling molecules that attract neutrophils and macrophages. Taking advantage of increased vessel permeability to enter injured tissues, these cells carry out additional phagocytosis and inactivation of microbes. The result is an accumulation of **pus**, a fluid rich in white blood cells, dead microbes, and cell debris.

A minor injury causes local inflammation, but severe tissue damage or infection may lead to a response that is systemic (throughout the body)—such as an increased production of

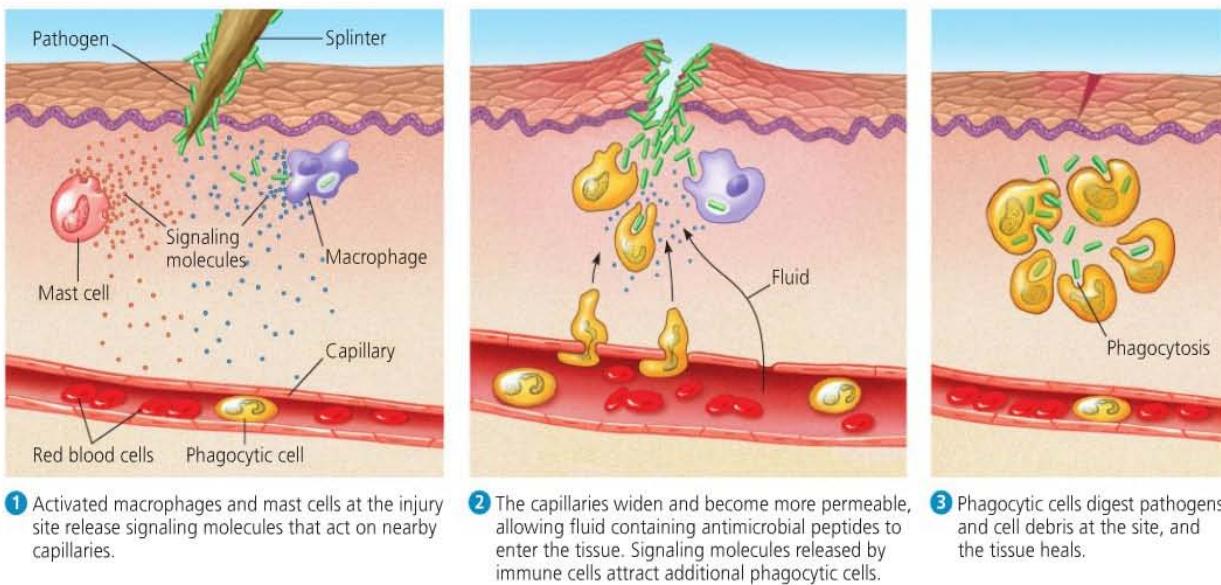
white blood cells. Cells in injured or infected tissue often secrete molecules that stimulate the release of additional neutrophils from the bone marrow. In a severe infection, such as meningitis or appendicitis, the number of white blood cells in the blood may increase several-fold within a few hours.

Another systemic inflammatory response is fever. Some toxins produced by pathogens, as well as substances called **pyrogens** released by activated macrophages, can reset the body's thermostat to a higher temperature (see Chapter 40). The benefits of the resulting fever are still a subject of debate. One hypothesis 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 flow, and low blood pressure, septic shock occurs most often in the very old and the very young. It is fatal in more than one-third of cases.

## Natural Killer Cells

**Natural killer (NK) cells** help recognize and eliminate certain diseased cells in vertebrates. With the exception of red blood cells, all cells in the body normally have on their surface a protein called a class I MHC molecule (we will say much more about this molecule shortly). Following viral infection or conversion to a cancerous state, cells sometimes stop expressing this protein. The NK cells that patrol the body attach to such stricken cells and release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.



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

## Innate Immune System Evasion 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 hides the polysaccharides of their cell walls, preventing recognition. One such bacterium, *Streptococcus pneumoniae*, played a critical role in the discovery that DNA can convey genetic information (see Figure 16.2). Among bacteria that do not avoid recognition, some are resistant to breakdown within lysosomes following phagocytosis. One example is the bacterium that causes tuberculosis (TB). Rather than being destroyed within the host's cells, such microbes grow and reproduce, effectively hidden from the innate immune defenses of the body. These and other mechanisms that prevent destruction by the innate immune system make the microbes that possess them substantial pathogenic threats: TB kills more than a million people a year worldwide.

### CONCEPT CHECK 43.1

1. What are the main advantages and disadvantages of relying on a physical barrier against infection?
2. Although pus is often seen simply as a sign of infection, it is also an indicator of immune defenses in action. Explain.
3. **WHAT IF?** If a microbe grew optimally at low pH, how might this affect its ability to act as a human pathogen? Explain.

For suggested answers, see Appendix A.

### CONCEPT 43.2

## In acquired immunity, lymphocyte receptors provide pathogen-specific recognition

Vertebrates are unique among animals in having acquired immunity in addition to innate immunity. B cells and T cells, types of white blood cells called **lymphocytes** (see Figure 42.17), are critical for this acquired immune defense. Like all blood cells, lymphocytes originate from stem cells in the bone marrow. Lymphocytes that migrate from the bone marrow to the **thymus**, an organ in the thoracic cavity above the heart, mature into **T cells** ("T" for thymus). Lymphocytes that mature in the bone marrow develop as **B cells**. (The "B" stands for the bursa of Fabricius, a bird organ where B cells were first discovered. But you can think of "B" as standing for bone marrow, where B cells mature in most vertebrates.)

B cells and T cells recognize and inactivate foreign cells and molecules. Both types of cells also contribute to *immunological memory*, an enhanced response to a foreign molecule encoun-

tered previously. Immunological memory, which can persist for many decades, is responsible for the protection we obtain against chickenpox and many other diseases from either a prior infection or vaccination. Its existence was apparent to the Greek historian Thucydides almost 2,400 years ago: He noted 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."

Although B cells and T cells function only in the acquired immune system, innate immunity and acquired immunity are not independent. At the start of an infection, signaling molecules from phagocytic cells carrying out innate immune responses activate lymphocytes, setting the stage for the slower-developing acquired response. For example, as macrophages and dendritic cells ingest microbes, these phagocytic cells secrete **cytokines**, proteins that help recruit and activate lymphocytes. Macrophages and dendritic cells also have a direct role in pathogen recognition by B cells and T cells, as you will see shortly.

### Acquired Immunity: An Overview

The basic facts of acquired immunity can be summarized by the following set of statements. Each B cell or T cell has on its surface many receptor proteins that can each bind a particular foreign molecule. The receptor proteins on a single lymphocyte are all the same, but there are millions of lymphocytes in the body that differ in the foreign molecules that their receptors recognize. When an animal is infected, B and T cells with receptors that can recognize the microbe are activated for particular roles in the immune response. In the activation process, the B and T cells interact with fragments of microbes displayed on the surface of cells. Activated lymphocytes undergo cell division, with a set of daughter cells being set aside to fight any future infections of the host by the same microbe. Some T cells assist in activating other lymphocytes. Other T cells detect and kill infected host cells. Specialized B cells secrete soluble receptor proteins that attack foreign molecules and cells circulating in body fluids.

Although the preceding paragraph is a fair summary of acquired immunity, it raises many questions: How are millions of different receptors made? How does infection activate the very lymphocytes that fight that infection? How does the immune system distinguish self from nonself? The answers to these questions and others will become clear as we explore acquired immunity in more detail, beginning with the process of recognition.

### Antigen Recognition by Lymphocytes

Any foreign molecule that is specifically recognized by lymphocytes and elicits a response from them is called an **antigen**. Most antigens are large molecules, either proteins or polysaccharides. Some antigens, such as toxins secreted by bacteria, are released into the extracellular fluid. Many other antigens protrude from the surface of pathogens or other foreign cells.

B cells and T cells recognize antigens using the antigen-specific receptors embedded in their plasma membranes (**Figure 43.9**). A single B or T lymphocyte has about 100,000 of these **antigen receptors** on its surface. B cells sometimes give rise to *plasma cells* that secrete a soluble form of the antigen receptor. This secreted protein is called an **antibody**, or **immunoglobulin (Ig)**.

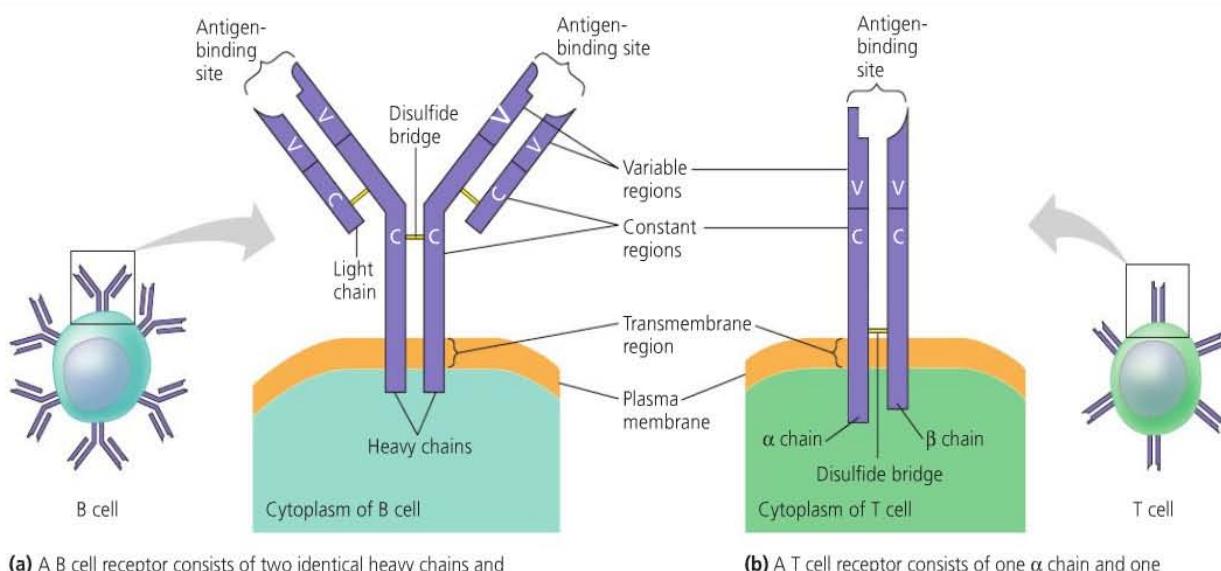
Antigen receptors and antibodies recognize just a small, accessible portion of an antigen that is called an **epitope**, or *antigenic determinant*. A single antigen usually has several different epitopes, each capable of inducing a response from a lymphocyte that recognizes the epitope (**Figure 43.10**).

All of the antigen receptors on a single lymphocyte are identical; that is, they recognize the same epitope. Each

of the body's lymphocytes thus displays *specificity* for a particular epitope. Consequently, each lymphocyte defends against any pathogen that produces molecules containing that epitope.

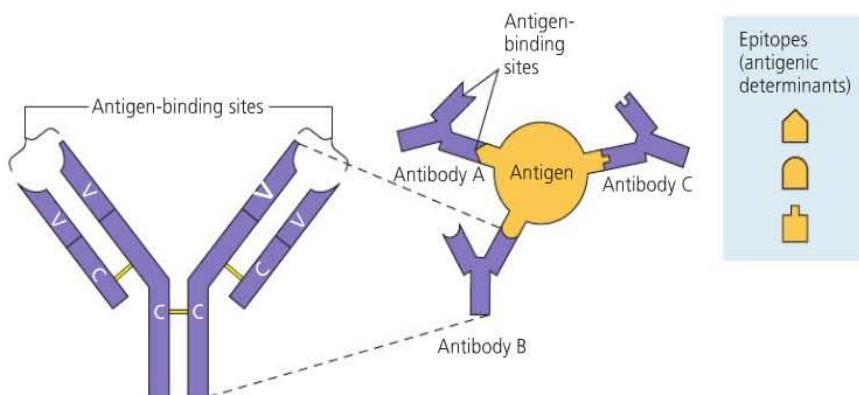
### The Antigen Receptors of B Cells and T Cells

Each **B cell receptor** for an antigen is a Y-shaped molecule consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains**, with disulfide bridges linking chains together (Figure 43.9a). 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 Antigen receptors on lymphocytes.** All the antigen receptors on a particular B cell or T cell are identical and bind identical antigens. The variable (V) regions of receptors vary extensively from cell to cell, accounting for the different binding specificities of individual lymphocytes; the constant (C) regions vary little or not at all.

**► Figure 43.10 Epitopes (antigenic determinants).** Only small, specific regions on antigens, called **epitopes**, are bound by the antigen receptors on lymphocytes and by secreted antibodies. In this example, three different antibody molecules bind to different epitopes on the same large antigen molecule. Note that epitopes and antigen-binding sites are typically irregular in shape, as illustrated for the antibody molecule on the left, but are often represented in a simplified, symmetrical manner, as illustrated for the antibodies on the right.



The light and heavy chains each have a *constant (C) region*, where amino acid sequences vary little among the receptors present 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 43.9a, each B cell receptor has two identical antigen-binding sites.

Antibodies have the same overall organization as B cell receptors, except that they lack the transmembrane region and cytoplasmic tail (see Figures 43.9 and 43.10). As a result, antibodies are secreted rather than membrane-bound, a difference associated with distinct functions that we will discuss shortly.

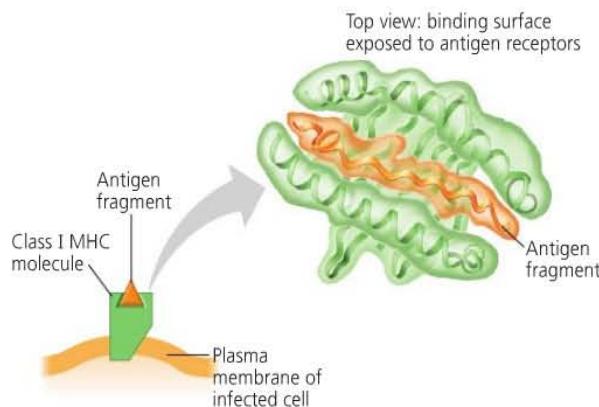
Each **T cell receptor** for an antigen consists of two different polypeptide chains, an  $\alpha$  chain and a  $\beta$  chain, linked by a disulfide bridge (Figure 43.9b). Despite having two rather than four chains, T cell receptors have many features in common with B cell receptors. Near the base of the 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  $\alpha$  and  $\beta$  chain variable (V) regions form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

B cell and T cell receptors have closely related but distinct functions. Both types of receptors bind to antigens via noncovalent bonds that stabilize the interaction between an epitope and the binding surface. In this manner, B cell receptors recognize and bind to an intact antigen, whether that antigen is free or on the surface of a pathogen. In contrast, T cell receptors bind only to antigen fragments that are displayed, or *presented*, on the surface of host cells. Each of the genes in a group called the **major histocompatibility complex (MHC)** produces a host cell protein that can present an antigen fragment to T cell receptors in this way. The simultaneous interaction of an antigen fragment, an MHC molecule, and a T cell receptor is a central event in acquired immunity and is our next topic.

### The Role of the MHC

Antigen recognition by T cells begins with a pathogen either infecting or being engulfed by a host cell. Once the pathogen is inside a host cell, enzymes in the cell cleave the pathogen proteins into smaller pieces, called peptide antigens or antigen fragments. These antigen fragments then bind to an MHC molecule inside the cell. Movement of the MHC molecule and bound fragment to the cell surface results in **antigen presentation**, the display of the antigen fragment on the cell surface (Figure 43.11). If an antigen-presenting cell encounters a T cell, the receptors on the T cell can bind to the antigen fragment.

Antigen presentation by MHC proteins either activates immune responses against the antigen or targets for destruction



**▲ Figure 43.11 Antigen presentation by an MHC molecule.**

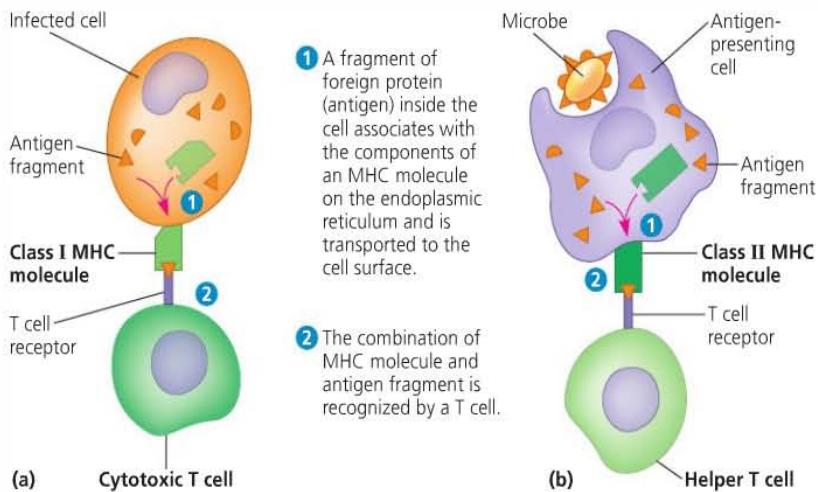
A class I MHC molecule extending from the plasma membrane displays a bound antigen fragment for recognition by the antigen receptor of a lymphocyte. The enlarged view is of the MHC surface that binds and presents an antigen fragment.

an infected cell displaying the antigen fragment. The type of cell that presents the antigen determines which kind of response occurs. When a phagocyte or lymphocyte that has engulfed a pathogen displays an antigen, it signals the immune system that an infection is under way. The immune system responds by increasing its response to that antigen and the pathogen that produces it. When a cell that has been invaded by a pathogen displays an antigen, it signals the immune system that the cell is infected. The immune system responds by eliminating such cells, disrupting further spread of the infection.

To recognize the type of cell displaying an antigen, the immune system relies on two classes of MHC molecules:

► **Class I MHC molecules** are found on almost all cells of the body (the notable exceptions being non-nucleated cells, such as red blood cells). Class I MHC molecules bind to peptide fragments of foreign antigens synthesized within the cell. Any body cell that becomes infected or cancerous can synthesize foreign antigens and display antigen fragments by virtue of its class I MHC molecules (Figure 43.12a). Class I MHC molecules displaying bound antigen fragments are recognized by a subgroup of T cells called **cytotoxic T cells**. The term *cytotoxic* refers to their use of toxic gene products to kill infected cells.

► **Class II MHC molecules** are made by just a few cell types, mainly dendritic cells, macrophages, and B cells. In these cells, class II MHC molecules typically bind to antigen fragment derived from foreign materials that have been internalized through phagocytosis or endocytosis (Figure 43.12b). Dendritic cells, macrophages, and B cells are known as **antigen-presenting cells** because of their key role in displaying such internalized antigens. Antigen-presenting cells display antigens for recognition by cytotoxic T cells and **helper T cells**, a group of T cells that assist both B cells and cytotoxic T cells.



◀ **Figure 43.12** The interaction of T cells with antigen-presenting cells.

(a) Class I MHC molecules display fragments of antigens to cytotoxic T cells.

(b) Class II MHC molecules display fragments of antigens to both cytotoxic T cells and, as shown here, helper T cells.

In both (a) and (b), the T cell receptor binds with an MHC molecule–antigen fragment complex. Class I MHC molecules are made by most nucleated cells, whereas class II MHC molecules are made primarily by antigen-presenting cells (macrophages, dendritic cells, and B cells).

## Lymphocyte Development

Now that you know how lymphocytes recognize antigens, let's consider three major properties of the acquired immune system. First, the tremendous diversity of receptors ensures that even pathogens never before encountered will be recognized as foreign. Second, this ability to recognize vast numbers of foreign molecules coexists with a lack of reactivity against the molecules that make up the animal's own cells and tissues. Third, the response to an antigen that has been encountered previously is stronger and more rapid than the initial response—a feature called immunological memory.

Three events in a lymphocyte's life provide the basis for receptor diversity, lack of self-reactivity, and immunological memory. The first two events take place as a lymphocyte matures. The third important event happens when a mature lymphocyte encounters and binds a specific antigen. Let's consider these three events in the order in which they occur.

### Generation of Lymphocyte Diversity by Gene Rearrangement

Differences in the amino acid sequence of the variable region account for the specificity of antigen receptors on lymphocytes. Recall that a single B or T cell displays about 100,000 antigen receptors, all identical. If we randomly selected any two B cells or T cells, it is highly unlikely that they would have the same antigen receptor. Instead, the variable regions at the tip of a particular antigen receptor would differ in their amino acid sequence from one cell to the other. Because the variable regions form the antigen-binding site, a particular amino acid sequence generates specificity for a certain epitope.

Each person has more than 1 million different B cells and 10 million different T cells, each with a particular antigen-binding specificity. Yet there are only about 20,500 protein-coding genes in the human genome. How, then, do we generate such remarkable diversity in antigen receptors? The answer lies in a

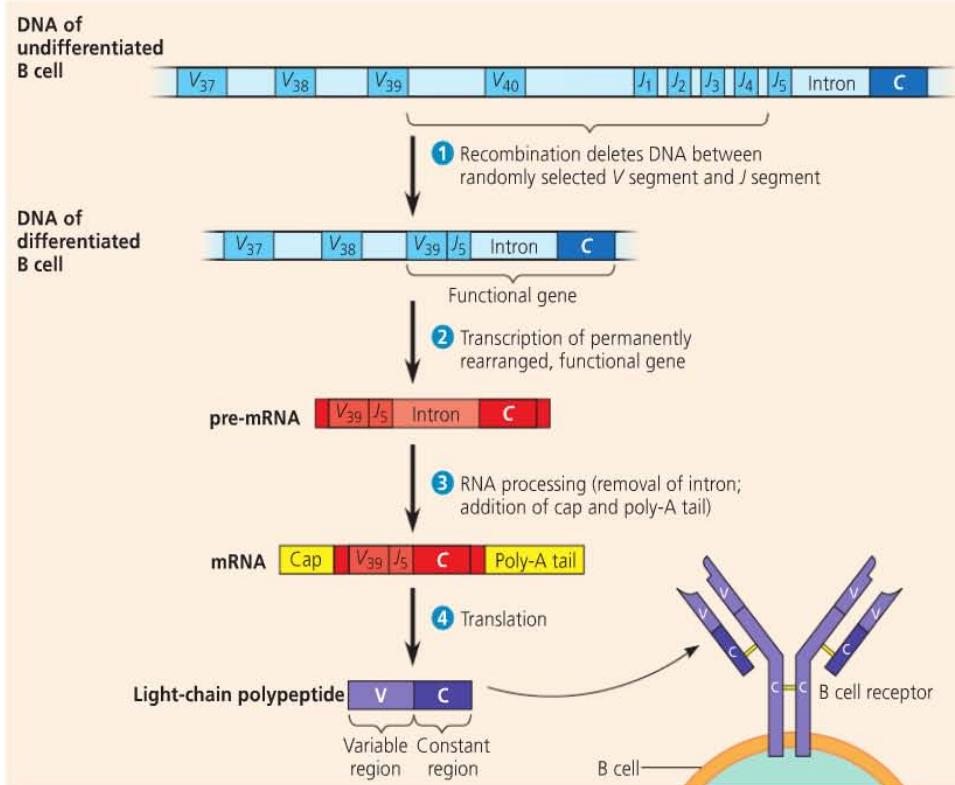
variety of combinations. Think of selecting a car with a choice of three interior colors and six exterior colors. There are 18 ( $3 \times 6$ ) color combinations to consider. Similarly, by combining variable elements, the immune system assembles many different receptors from a much smaller collection of parts.

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

The capacity to generate diversity is built into the structure of the Ig light-chain gene. 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 entire constant region. DNA sequencing reveals that 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 series (Figure 43.13, on the next page). Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 ( $40 V \times 5 J \times 1 C$ ) different ways. (The number of different heavy-chain genes is even greater.)

Assembling a functional light-chain gene requires rearranging the DNA. Early in B cell development, a set of enzymes collectively called recombinase links one *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 will be joined after transcription by splicing out the intervening RNA (see Figure 17.10 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



**Figure 43.13**  
**Immunoglobulin (antibody) gene rearrangement.** The joining of randomly selected *V* and *J* gene segments (*V<sub>39</sub>* and *J<sub>5</sub>* in this example) results in a functional gene that encodes the light-chain polypeptide of a B cell 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 body cells have exactly the same DNA.

undergo a similar rearrangement. In any given cell, however, only one light-chain gene and one 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 surface. For the total population of B cells in a human body, the number of such combinations has been calculated as  $1.65 \times 10^6$ . Furthermore, mutations introduced during *VJ* recombination add additional variation, making the number of possible antigen-binding specificities even greater.

### Origin of Self-Tolerance

Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the body'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. Lymphocytes with receptors specific for the body's own molecules are typically either de-

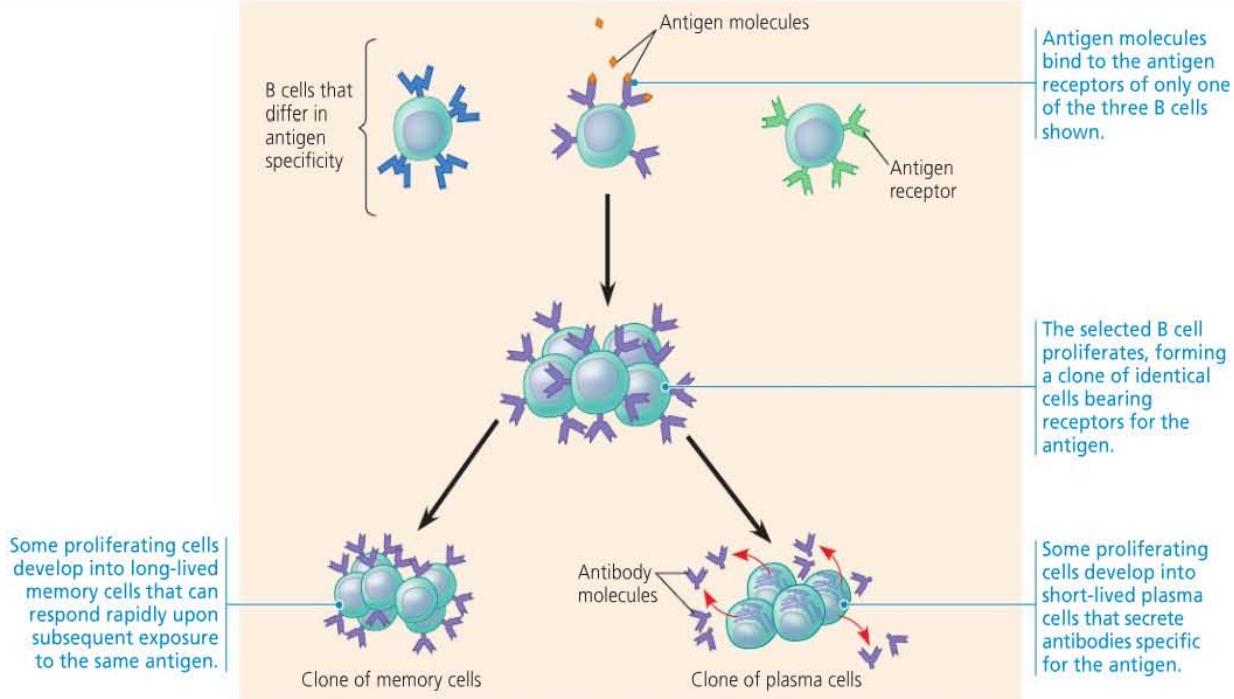
stroyed by apoptosis or rendered nonfunctional, leaving only those that react to foreign molecules. Since the body normally lacks mature lymphocytes that can react against its own components, the immune system is said to exhibit *self-tolerance*. As you will read later, failure of self-tolerance can lead to autoimmune diseases, such as multiple sclerosis.

### Amplifying Lymphocytes by Clonal Selection

Because the body contains an enormous variety of antigen receptors, only a tiny fraction are specific for the epitopes on a given antigen. As a result, it is very rare for an antigen to encounter a lymphocyte with a receptor specific for that antigen. How, then, can the acquired immune response be so effective? The answer lies in the changes in cell number and behavior triggered by the binding of antigen to lymphocyte.

The binding of an antigen receptor to its specific antigen initiates events that activate the lymphocyte. Activated B cells or T cells amplify the response by dividing many times, forming two types of clones: effector cells and memory cells. **Effector cells**, which are short-lived, attack the antigen and any pathogens producing that antigen. **Memory cells**, which are long-lived but less numerous, bear receptors specific for the antigen.

The proliferation of a lymphocyte into a clone of cells in response to binding an antigen is called **clonal selection** (Figure 43.14). This concept is so fundamental to understanding acquired immunity that it is worth restating: The presentation of an antigen to specific receptors on a lymphocyte



leads to repeated rounds of cell division. The result is a clonal population of thousands of cells, all specific for that antigen.

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 represents the **primary immune response**. The primary response peaks about 10 to 17 days after the initial exposure. During this time, selected B cells generate antibody-secreting effector B cells, called **plasma cells**, and selected T cells are activated to their effector forms, consisting of helper cells and cytotoxic cells. If an individual is exposed again to the same antigen, the response is faster (typically peaking only 2 to 7 days after exposure), of greater magnitude, and more prolonged. This is the **secondary immune response**. Measures of antibody concentrations in blood serum over time clearly show the difference between primary and secondary immune responses (**Figure 43.15**).

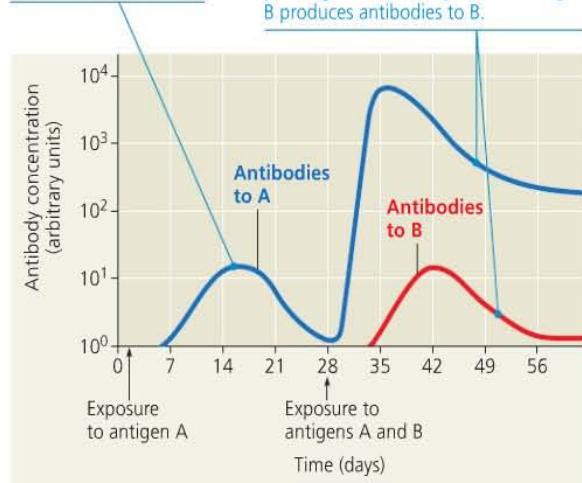
The secondary immune response relies on the reservoir of T and B memory cells generated following initial exposure to an antigen. Because these cells are long-lived, they provide the basis for immunological memory that can span many decades. If and when an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of large clones of effector cells and thus 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 will explore next.

**▲ Figure 43.14 Clonal selection of B cells.** In response to its specific antigen and immune cell signals, a B cell divides and forms a clone of cells. Some of these cells become memory B cells; others become antibody-secreting plasma cells. T cells specific for the antigen undergo a similar process, generating memory T cells and effector T cells. Lymphocytes with a different antigen specificity (represented in this figure by different shapes and colors of the receptors) do not respond.

**Primary immune response**  
to antigen A produces antibodies to A.

**Secondary immune response**  
to antigen A produces antibodies to A;  
**primary immune response** to antigen B produces antibodies to B.



**▲ 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).

## CONCEPT CHECK 43.2

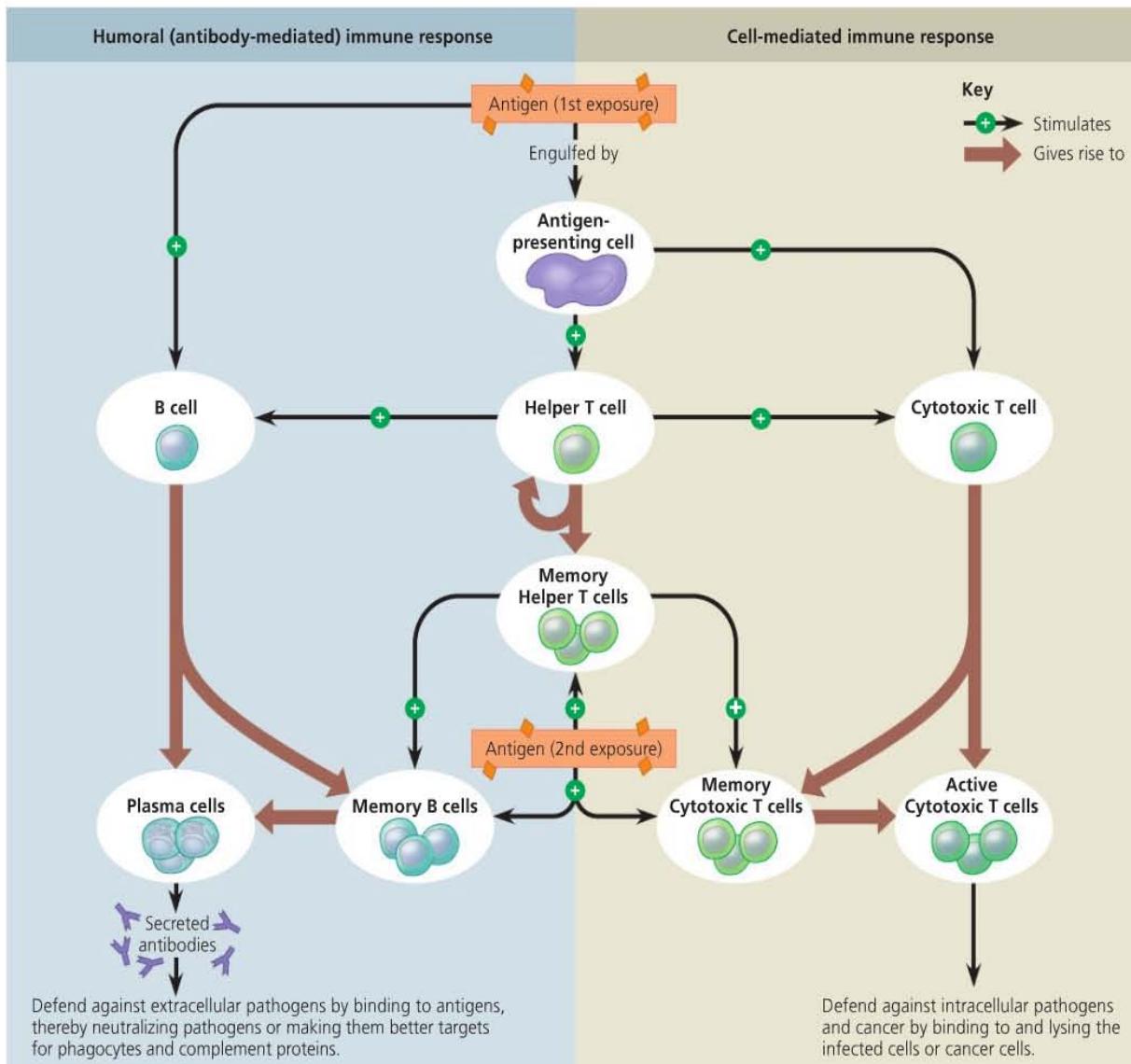
- DRAW IT** Sketch a B cell receptor. Label the V and C regions of the light and heavy chains. Now mark the positions of the antigen-binding sites, disulfide bridges, and transmembrane regions. How do the positions of these features relate to the location of the variable and constant regions?
- Explain two advantages of having memory cells when a pathogen is encountered for a second time.
- WHAT IF?** If both copies of a light-chain gene and a heavy-chain gene recombined in each B cell, how would this affect B cell development?

For suggested answers, see Appendix A.

## CONCEPT 43.3

### Acquired immunity defends against infection of body cells and fluids

Acquired immunity is based on both a humoral immune response and a cell-mediated immune response (Figure 43.16). The **humoral immune response** involves the activation and clonal selection of effector B cells, which secrete antibodies that circulate in the blood and lymph. The humoral response is so named because blood and lymph were long ago called body humors. It is also called the antibody-mediated response because of the key role of antibodies. The predominant **cell-mediated immune response** involves the activation and



▲ **Figure 43.16** An overview of the acquired immune response.

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

clonal selection of cytotoxic T cells, which identify and destroy the target cells. A third population of lymphocytes, the helper T cells, aids both responses. As we examine the cellular interactions that underlie the acquired immune response, you can refer to the diagram in Figure 43.16 to appreciate how these interactions work together.

### Helper T Cells: A Response to Nearly All Antigens

Activated by encounters with antigen-presenting cells, helper T cells play a central role in enhancing humoral and cell-mediated responses. The helper T cell proliferates after interacting with antigen fragments displayed by antigen-presenting cells (usually dendritic cells). The resulting clone of cells differentiates into activated helper T cells and memory helper T cells. Activated helper T cells secrete cytokines that stimulate the activation of nearby B cells and cytotoxic T cells.

A helper T cell and the antigen-presenting cell displaying its specific epitope have a complex interaction (Figure 43.17). The T cell receptors on the surface of the helper T cell bind to the antigen fragment that is held by a class II MHC molecule on the antigen-presenting cell. At the same time, a protein called CD4, found on the surface of most helper T cells, binds to the class II MHC molecule. CD4 helps keep the helper T cell and antigen-presenting cell joined. As the two cells interact, signals in the form of cytokines are exchanged in both directions. For example, 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. The net result is activation of the helper T cell.

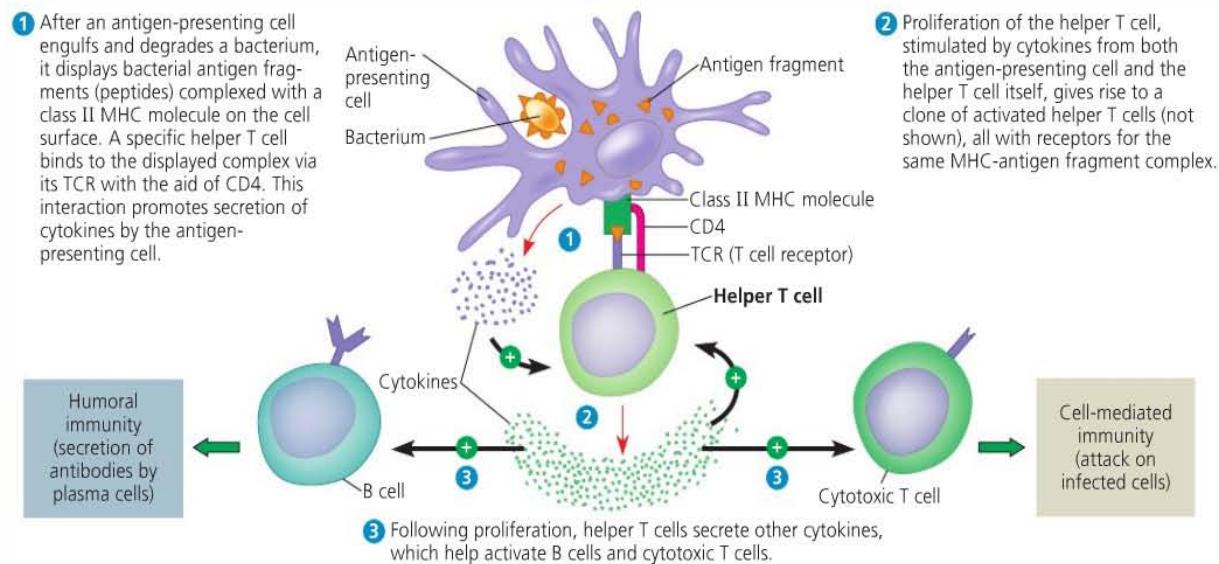
The three principal types of antigen-presenting cells—dendritic cells, macrophages, and B cells—interact with helper T cells in different contexts. Dendritic cells are particularly important in triggering a primary immune response. They serve

as sentinels in the epidermis and other tissues frequently exposed to foreign antigens. After dendritic cells capture antigens, they migrate from the infection site to lymphoid tissues. There they present antigens, via class II MHC molecules, to helper T cells (see Figure 43.17). Macrophages play the key role in initiating a secondary immune response by presenting antigens to memory helper T cells, while the humoral response relies mainly on B cells to present antigens to helper T cells.

### Cytotoxic T Cells: A Response to Infected Cells

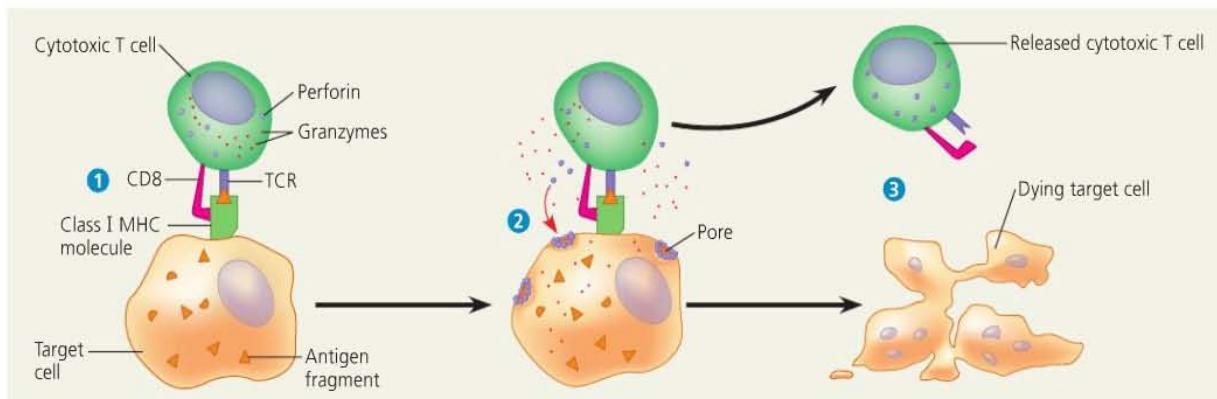
Cytotoxic T cells are the effector cells in a cell-mediated immune response. To become active, they require signaling molecules from helper T cells as well as interaction with an antigen-presenting cell. Once activated, they can eliminate cancerous body cells and body cells infected by viruses or other intracellular pathogens. Fragments of nonself proteins synthesized in such target cells associate with class I MHC molecules and are displayed on the cell surface, where they can be recognized by cytotoxic T cells (Figure 43.18, on the next page). A surface protein called CD8, found on most cytotoxic T cells, enhances the interaction between a target cell and a cytotoxic T cell. Binding of CD8 to a class I MHC molecule helps keep the two cells in contact while the cytotoxic T cell is activated. Thus, the roles of class I MHC molecules and CD8 are similar to those of class II MHC molecules and CD4.

The targeted destruction of an infected cell by a cytotoxic T cell involves the secretion of proteins that cause cell rupture and cell death (see Figure 43.18). The death of the infected cell not only deprives the pathogen of a place to reproduce but also exposes it to circulating antibodies, which mark it for disposal. After destroying an infected cell, the cytotoxic T cell may move on and kill other cells infected with the same pathogen.



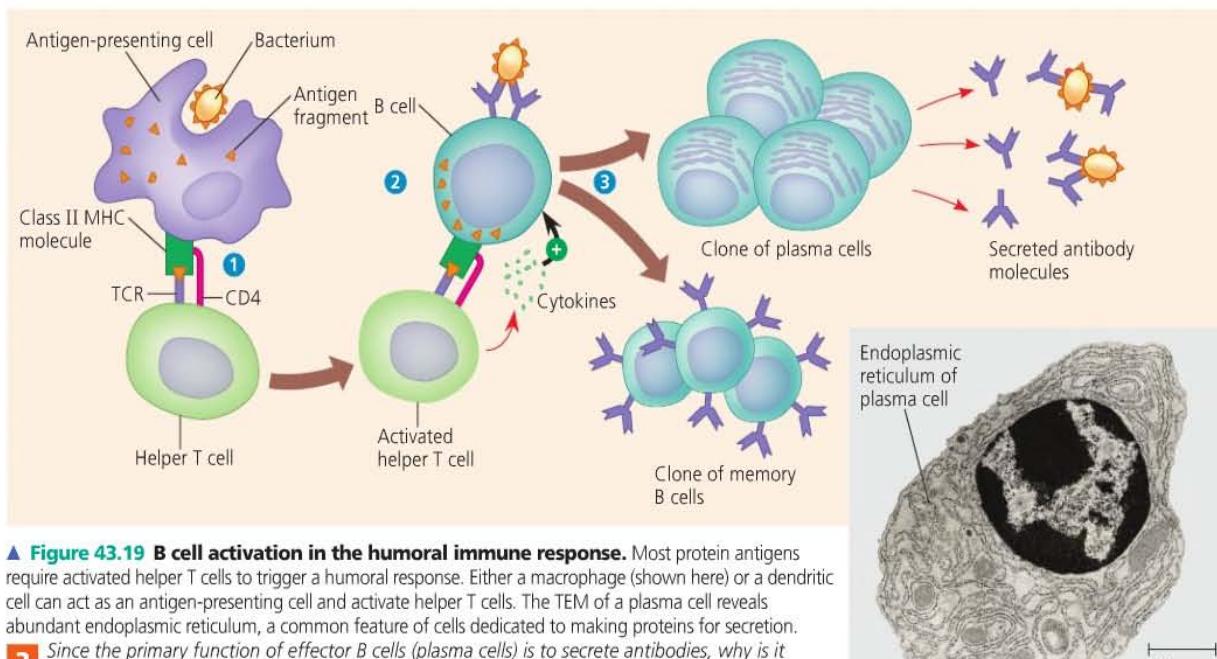
▲ Figure 43.17 The central role of helper T cells in humoral and cell-mediated immune responses.

- An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on a target cell via its TCR with the aid of the protein CD8.
- The T cell releases perforin molecules, which form pores in the target cell membrane, and granzymes, enzymes that break down proteins. Granzymes enter the target cell by endocytosis.
- The granzymes initiate apoptosis within the target cell, leading to fragmentation of the nucleus and cytoplasm and eventual cell death. The released cytotoxic T cell can attack other target cells.



**▲ Figure 43.18 The killing action of cytotoxic T cells.** An activated cytotoxic T cell releases molecules that make pores in a target cell's membrane and enzymes that break down proteins, promoting the cell's death.

- After an antigen-presenting cell engulfs and degrades a bacterium, it displays an antigen fragment (peptide) 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, forming a clone of activated helper T cells (not shown).
- A B cell with receptors for the same peptide internalizes the antigen and displays it on the cell surface in a complex with a class II MHC protein. An activated helper T cell bearing receptors specific for the displayed antigen fragment binds to the B cell. This interaction, with the aid of cytokines from the T cell, activates the B cell.
- The activated B cell proliferates and differentiates into antibody-secreting plasma cells and memory B cells. The secreted antibodies are specific for the same bacterial antigen that initiated the response.



**▲ Figure 43.19 B cell activation in the humoral immune response.** Most protein antigens require activated helper T cells to trigger a humoral response. Either a macrophage (shown here) or a dendritic cell can act as an antigen-presenting cell and activate helper T cells. The TEM of a plasma cell reveals abundant endoplasmic reticulum, a common feature of cells dedicated to making proteins for secretion.

**? Since the primary function of effector B cells (plasma cells) is to secrete antibodies, why is it important that memory B cells have cell-surface antigen receptors?**

## B Cells: A Response to Extracellular Pathogens

The secretion of antibodies by clonally selected B cells is the hallmark of the humoral response (**Figure 43.19**). Activation of

this response typically involves B cells and helper T cells, as well as proteins on the surface of bacteria. As depicted in Figure 43.19, B cell activation by an antigen is aided by cytokines se-

creted from helper T cells that have encountered the same antigen. Stimulated by both an antigen and cytokines, the B cell proliferates and differentiates into a clone of antibody-secreting plasma cells and a clone of memory B 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 of the foreign molecules by receptor-mediated endocytosis (see Figure 7.20). The B cell then presents an MHC-antigen fragment complex to a helper T cell. This achieves the direct cell-to-cell contact that is usually critical to B cell activation (see step 2 in Figure 43.19).

B cell activation leads to a robust humoral response: An activated B cell gives rise to a clone of thousands of plasma cells, each of which secretes approximately 2,000 antibody molecules 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 clones of plasma cells directed against different epitopes on the common antigen.

For antigens, including polysaccharides, that contact multiple receptors on a single cell, a B cell response can occur without the involvement of cytokines or helper T cells. Although such responses generate no memory B cells, they play an important role in defending against many bacteria.

### Antibody Classes

For a given B cell, the antibodies produced differ from the B cell receptor only in the constant (C) region of the heavy chain. In place of a transmembrane region and cytoplasmic tail, the heavy chain contains sequences that determine where the antibody is distributed and how it mediates antigen disposal.

The five major types of heavy-chain C regions determine five major classes of antibodies. **Figure 43.20** summarizes the structures and functions of these antibody classes. Changes in the heavy-chain gene that switch B cells from production of one antibody class to another occur only in response to antigen stimulation and to specific regulatory signals from T cells.

The power of antibody specificity and antigen-antibody binding has been harnessed in laboratory research and clinical diagnosis. Some antibody tools are *polyclonal*: They are the products of many different clones of B cells, each specific for a different epitope. Antibodies produced following 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. All the **monoclonal antibodies** produced by such a culture are identical and specific for the same epitope on an antigen. Monoclonal antibodies are particularly

Class of Immunoglobulin (Antibody)	Distribution	Function
IgM (pentamer)	First Ig class produced after initial exposure to antigen; then its concentration in the blood declines	Promotes neutralization and cross-linking of antigens; very effective in complement system activation (see Figure 43.21)
IgG (monomer)	Most abundant Ig class in blood; also present in tissue fluids	Promotes opsonization, neutralization, and cross-linking of antigens; less effective in activation of complement system than IgM (see Figure 43.21)
		Only Ig class that crosses placenta, thus conferring passive immunity on fetus
IgA (dimer)	Present in secretions such as tears, saliva, mucus, and breast milk	Provides localized defense of mucous membranes by cross-linking and neutralization of antigens (see Figure 43.21)
Secretory component		Presence in breast milk confers passive immunity on nursing infant
IgE (monomer)	Present in blood at low concentrations	Triggers release from mast cells and basophils of histamine and other chemicals that cause allergic reactions (see Figure 43.23)
IgD (monomer)	Present primarily on surface of B cells that have not been exposed to antigens	Acts as antigen receptor in the antigen-stimulated proliferation and differentiation of B cells (clonal selection)
Trans-membrane region		

▲ **Figure 43.20 The five antibody, or immunoglobulin (Ig), classes.** All antibody classes consist of similar Y-shaped molecules in which the tail region determines the distribution and functions characteristic of each class. IgM and IgA antibodies contain a J chain (unrelated to the J gene segment) that helps hold the subunits together. As an IgA antibody is secreted across a mucous membrane, it acquires a secretory component that protects it from cleavage by enzymes.

useful for tagging specific molecules. 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 provides a reliable indicator for a very early stage of pregnancy.

### The Role of Antibodies in Immunity

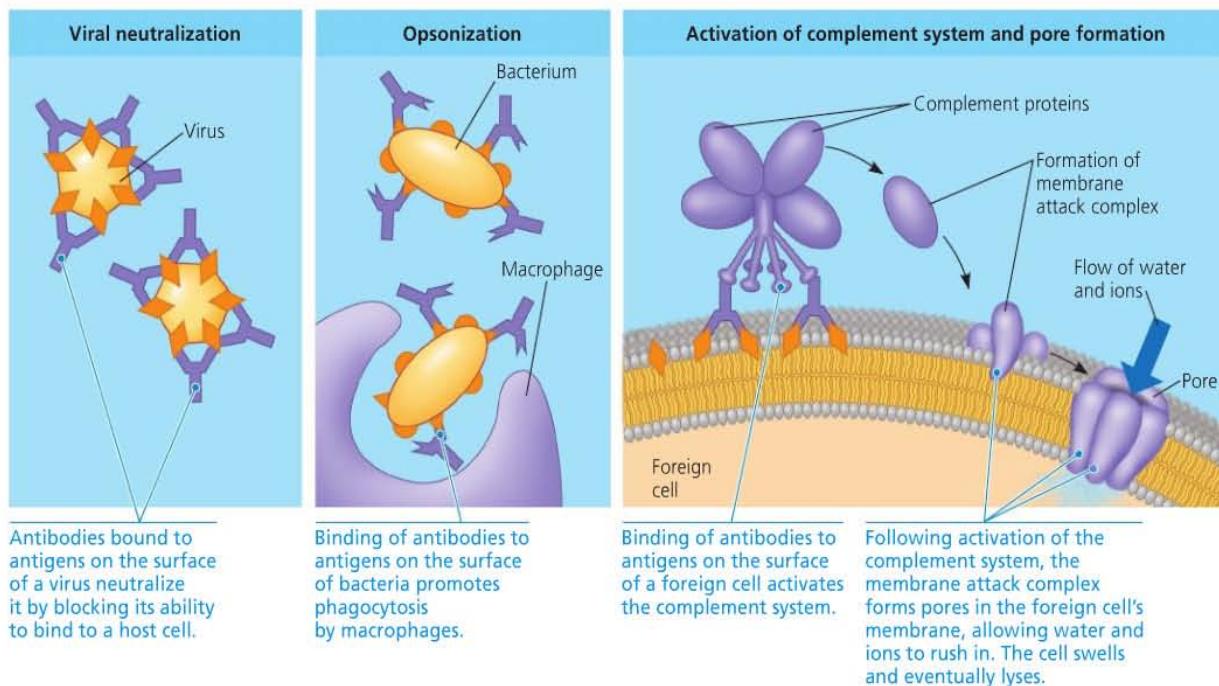
The binding of antibodies to antigens can interfere with pathogen function in many ways, some of which are diagrammed in **Figure 43.21**. In the simplest of these, **neutralization**, antibodies bind to surface proteins of a virus or bacterium, thereby blocking the pathogen's ability to infect a host cell. Similarly, antibodies sometimes bind to and neutralize toxins released in body fluids. In a process called **opsonization**, the antibodies bound to antigens present a readily recognized structure for macrophages and therefore increase phagocytosis. Because each antibody has two antigen-binding sites, antibodies can also facilitate phagocytosis by linking bacterial cells, virus particles, or antigens 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 antigen-antibody complexes on a microbe or foreign cell to one

of the complement proteins triggers a cascade in which each protein of the complement system activates the next. 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 (see Figure 43.21, right). Whether activated as part of innate or acquired defenses, this cascade of complement protein activity results in the lysis of microbes and produces factors that promote inflammation or stimulate phagocytosis.

When antibodies facilitate phagocytosis (see Figure 43.21, 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 the innate and acquired immune systems contributes to a coordinated, effective response to infection.

Although antibodies are the cornerstones 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 the exposed proteins, the presence of bound antibody at the cell surface can recruit a natural killer cell. The NK cell then releases proteins that cause the infected cell to undergo apoptosis.



▲ **Figure 43.21 Antibody-mediated mechanisms of antigen disposal.** The binding of antibodies to antigens marks microbes, foreign particles, and soluble antigens for inactivation or destruction.

## Active and Passive Immunization

Our discussion of acquired immunity has to this point focused on the defenses that arise when a particular microbe infects the body. In response to infection, clones of memory cells form, providing **active immunity**. In contrast, a distinct type of immunity results when the IgG antibodies of a pregnant woman cross the placenta to her fetus. The transferred antibodies are poised to immediately help destroy any pathogens for which they are specific. This protection is called **passive immunity** because the antibodies provided by the mother guard against microbes that have never infected the newborn. Because passive immunity does not involve the recipient's B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months). However, IgA antibodies are passed from a mother to her infant in breast milk (**Figure 43.22**). These antibodies provide additional protection against infection while the infant's immune system develops.

Both active immunity and passive immunity can be induced artificially. Active immunity can develop from the introduction of antigens into the body through **immunization**, often called **vaccination**. The virus causing cowpox, a mild disease usually seen in cows, was used over two centuries ago as the first vaccine (from the Latin *vacca*, cow). Vaccination with cowpox was significant because it enhanced the immune response to the closely related and far more dangerous smallpox virus. Today, many sources of antigen are used to make vaccines, including inactivated bacterial toxins, killed microbes, parts of microbes, weakened microbes 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 response.

Vaccination programs have been successful against many infectious diseases that once killed, crippled, or incapacitated large numbers of people. A worldwide vaccination campaign led to eradication of smallpox in the late 1970s. In industrialized countries, 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. Even in developed countries, the failure of some parents to immunize children with available vaccines has led to sporadic outbreaks of serious but fully preventable diseases. For example, a decline in vaccination rates within the former Soviet Union led to an outbreak of diphtheria during the mid-1990s that resulted in over 5,000 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



◀ **Figure 43.22**  
**Passive immunization**  
**of an infant occurs**  
**during breast-feeding.**

treated with antivenin, a serum from sheep or horses that have been immunized against the venom of one or more species of poisonous snakes. When injected immediately after a snakebite, the antibodies in antivenin can neutralize toxins in the venom before the toxins do massive damage.

## Immune Rejection

Like pathogens, cells from another person can be recognized 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. (It remains something of a puzzle why a pregnant woman does not reject her fetus as nonself tissue.) Keep in mind that the body's hostile reaction to a transplant of other tissues or whole organs or to an incompatible blood transfusion is the expected reaction of a healthy immune system exposed to foreign antigens.

## Blood Groups

To avoid harmful immune reactions in human blood transfusions, ABO blood groups must be taken into account. As discussed in Chapter 14, red blood cells are designated as type A if they have A antigen molecules on their surface. Similarly, the B antigen is found on type B red blood cells; both A and B antigens are found on type AB red blood cells; and neither antigen 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 blood group antigens. By responding to the bacterial epitope similar to B antigen, a person with type A blood makes antibodies that can react with B antigen. No antibodies are made against the bacterial epitope similar to A antigen, since lymphocytes reactive with self antigens 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 can act against the recipient's type A red blood cells.

### Tissue and Organ Transplants

In the case of tissue and organ transplants, or grafts, it is MHC molecules that stimulate the immune response that leads to rejection. Each vertebrate species has many different alleles for each class I and class II MHC gene, enabling presentation of antigen fragments that vary in shape and 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 try to 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. However, these medicines can leave the recipient more susceptible to infections during the course of treatment.

In a bone marrow transplant between individuals, the problem of rejection is reversed: The donor tissue can reject the recipient's body tissues. 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

- If a child were born without a thymus, what cells and functions would be deficient? Explain.
- 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?
- WHAT IF?** Suppose that a snake handler bitten by a particular venomous snake species was treated with antivenin. Why might the treatment for a second such bite be different?

For suggested answers, see Appendix A.

### CONCEPT 43.4

## Disruptions in immune system function can elicit or exacerbate disease

Although acquired 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 the acquired immune system is blocked or misregulated. We'll then turn to some of the evolutionary adaptations of pathogens that diminish the effectiveness of host immune responses.

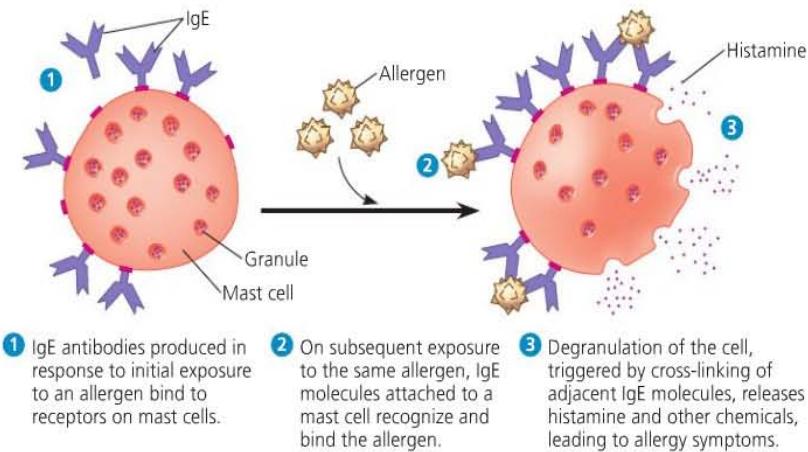
### Exaggerated, Self-Directed, and Diminished Immune Responses

The highly regulated interplay among lymphocytes, 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 (see Figure 43.20). Hay fever, for instance, occurs when plasma cells secrete IgE antibodies specific for antigens on the surface of pollen grains (**Figure 43.23**). Some of these antibodies attach by their base to mast cells in connective tissues. Later, when pollen grains again enter the body, they attach to the antigen-binding sites of IgE on the surface of mast cells. Interaction with the large pollen grains cross-links adjacent IgE molecules, inducing the mast cell to release histamine and other inflammatory agents from granules (vesicles), a process called *degranulation*. Recall that histamine causes dilation and increased permeability of small blood vessels. Such vascular changes lead to typical allergy symptoms: sneezing, runny nose, tearing 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 mast cell degranulation triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure. Death may occur within minutes. 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 other foods can die from ingesting only tiny amounts of these



▲ **Figure 43.23** Mast cells, IgE, and the allergic response.

allergens. People with severe hypersensitivities often carry syringes containing the hormone epinephrine, which counters this allergic response.

### Autoimmune Diseases

In some people, the immune system turns against particular molecules of the body, causing an **autoimmune disease**. This loss of self-tolerance can take 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 antibody-mediated autoimmune disease, *rheumatoid arthritis*, leads to damage and painful inflammation of the cartilage and bone of joints (Figure 43.24). 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 an autoimmune disease—*multiple sclerosis*. In this disease, T cells infiltrate the central nervous system, leading to destruction of the myelin sheath that surrounds parts of many neurons (see Figure 48.12).



▲ **Figure 43.24** X-ray of a hand 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 as likely as men to suffer from multiple sclerosis and rheumatoid arthritis and nine times more likely to develop lupus. There has been substantial progress in the field of autoimmunity. For example, we now know that regulatory T cells ordinarily help prevent attack by any self-reactive lymphocytes that remain functional in adults. Nevertheless, 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. 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.

### Immunodeficiency Diseases

A disorder in which the ability of an immune system to protect against pathogens 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 acquired defenses—or both—may be impaired. In severe combined immunodeficiency (SCID), functional lymphocytes are rare or absent. Lacking an acquired immune response, SCID patients are susceptible to recurrent 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. The immune system is also suppressed by certain cancers, 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**, or AIDS, which is caused by a virus. We will discuss AIDS further in the next section, which focuses on how pathogens escape the acquired immune response.

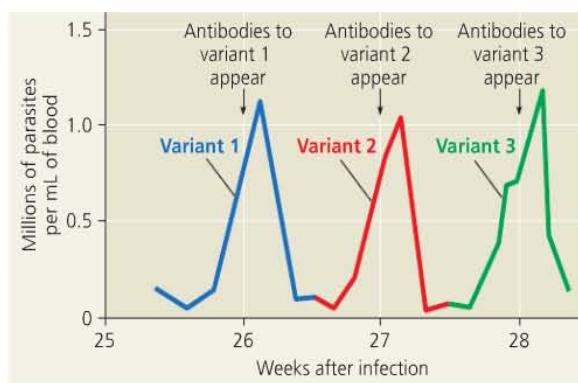
### Acquired Immune System Evasion by Pathogens

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 acquired immune response (**Figure 43.25**).

Antigenic variation is the major reason the influenza, or "flu," virus remains a major public health problem. As it replicates in



▲ **Figure 43.25** 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 acquired immune response.

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 the human population completely recognize the new strain. Such an event caused the influenza outbreak of 1918–1919, which killed more than half a million people in the United States. Worldwide more than 20 million people died, a greater number than had died in World War I. Today, a very potent form of an avian influenza virus poses the threat of another devastating outbreak (see Chapter 54).

#### Latency

Some viruses remain in a host without activating immune defenses, ceasing production of viral products targeted by lymphocytes. In this largely inactive state called *latency*, there are typically no free virus particles. Instead, 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 circumstances trigger the synthesis and release of 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 and infection of 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 acquired 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 cell's CD4 molecules. However, HIV also infects some cell types that have low levels of CD4, including macrophages and brain cells. Within the cell, the HIV RNA

genome is reverse-transcribed, and the product DNA is integrated into the host cell's genome. In this form, the viral genome can direct production of new virus particles (see Figure 19.8).

Although the body responds to HIV with an aggressive 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 prevent recognition and elimination by the immune system. 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 an infected cell but does not produce new virus proteins or particles, it is shielded from surveillance by the immune system. 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 acquired immune response but also abolishes it (Figure 43.26). The damaging effects of viral reproduction and cell death triggered by the virus leads to loss of T cells, impairing both humoral and cell-mediated immune responses. The result is a susceptibility to infections and cancers that a healthy immune system would most of the time defeat. For example, *Pneumocystis carinii* is a common fungus that does not cause disease in healthy individuals but can result in severe pneumonia in people with AIDS. Likewise, the Kaposi's sarcoma herpes virus 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 cause of death in AIDS patients.

At present, HIV infection cannot be cured, although certain drugs can slow HIV reproduction and the progression to AIDS. 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 is reduced by the use of a

combination of drugs; viruses newly resistant to one drug can be defeated by another. But the appearance of strains resistant to multiple drugs reduces the effectiveness of multidrug "cocktails" in some patients. Frequent mutations in HIV surface antigen genes also have hampered efforts to develop an effective vaccine. Worldwide, the AIDS epidemic continues to grow. In 2006, more than 2.5 million people died of AIDS, with the disease now being 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 or blood. Unprotected sex (that is, without a condom) and transmission via HIV-contaminated needles (typically among intravenous drug users) account for nearly all 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 transmit the disease most readily in the first few weeks of infection, before they express HIV-specific antibodies that can be detected in a blood test.

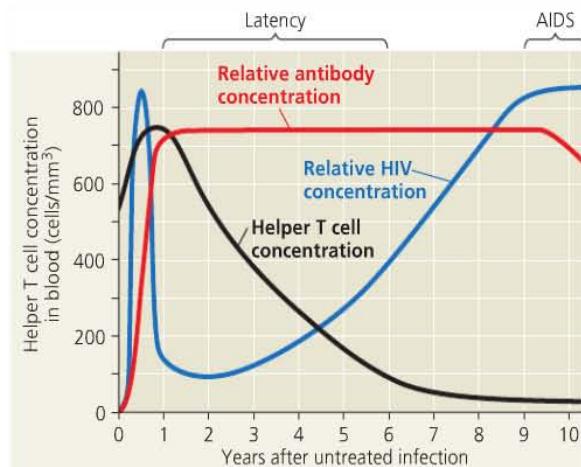
## Cancer and Immunity

The relationship between the immune response and cancer remains only partially understood. It is clear that the frequency of certain cancers increases when the immune response is impaired. This observation has led to the suggestion that the immune system normally attacks body cells that become cancerous. However, there is an alternative explanation. Impairment of the immune response leaves the body open to infection, which causes inflammatory responses. Inflammation, in turn, is now known to be a condition contributing to the development of many cancers. Therefore, it may be that the immune system does not fight cancer effectively, and its impairment leads to increased cancer as the result of increased inflammation. Determining how cancer and immunity are linked and whether passive or active immunization can be used to fight cancer remain active areas of investigation.

### CONCEPT CHECK 43.4

1. In myasthenia gravis, antibodies bind to and block acetylcholine receptors at neuromuscular junctions, 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 acquired defenses?

For suggested answers, see Appendix A.



▲ Figure 43.26 The progress of an untreated HIV infection.

# Chapter 43 Review



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## SUMMARY OF KEY CONCEPTS

### CONCEPT 43.1

**In innate immunity, recognition and response rely on shared traits of pathogens (pp. 931–936)**

- ▶ **Innate Immunity of Invertebrates** Invertebrates are protected by physical and chemical barriers as well as cell-based defenses. In insects, microbes that penetrate barrier defenses are ingested by cells in the hemolymph that also release antimicrobial peptides. Activation of innate immune responses to a pathogen class relies on recognition proteins.
- ▶ **Innate Immunity of Vertebrates** Intact skin and mucous membranes form barriers to microbes. 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 phagocytes, which help trigger an inflammatory response. Complement proteins, interferons, and other antimicrobial proteins also act against microbes. In local inflammation, histamine and other chemicals released from injured cells promote changes in blood vessels that allow fluid, more phagocytes, and antimicrobial proteins to enter tissues. Natural killer (NK) cells can induce the death of virus-infected cells.
- ▶ **Innate Immune System Evasion by Pathogens** The outer capsule of some bacteria prevents recognition. Some bacteria are resistant to breakdown within lysosomes.

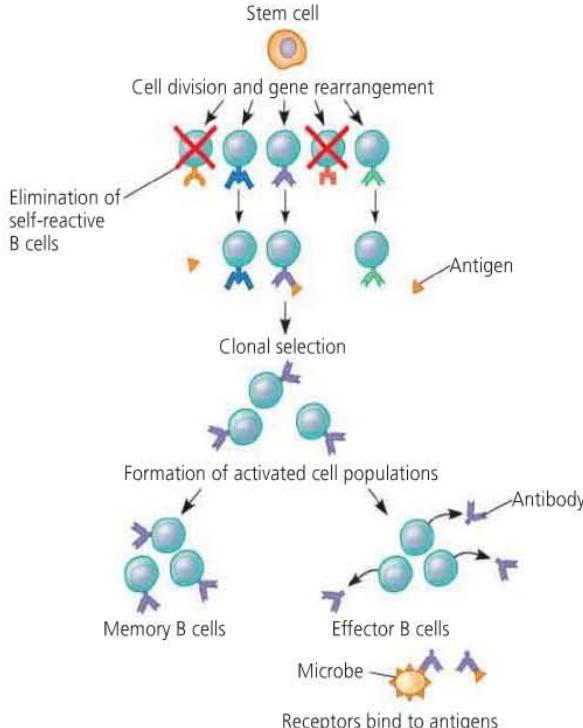
### CONCEPT 43.2

**In acquired immunity, lymphocyte receptors provide pathogen-specific recognition (pp. 936–942)**

- ▶ Acquired 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).
- ▶ **Acquired Immunity: An Overview** Lymphocytes have cell-surface receptors for foreign molecules. All receptor proteins on a single lymphocyte are the same, but there are millions of lymphocytes in the body that differ in the foreign molecules that their receptors recognize. Upon infection, B and T cells specific for the microbe are activated. Some T cells help other lymphocytes; others kill infected host cells. B cells produce soluble receptor proteins that inhibit foreign molecules and cells. Some activated lymphocytes defend against future infections by the same microbe.
- ▶ **Antigen Recognition by Lymphocytes** Variable regions of receptors bind to small regions of an antigen (epitopes). B cells recognize epitopes in intact antigens. T cells recognize epitopes in small antigen fragments (peptides) complexed with cell-surface proteins called major histocompatibility (MHC) molecules. Class I MHC molecules, located on all nucleated cells, display antigen fragments to cytotoxic T cells. Class II MHC molecules, located mainly on dendritic cells, macrophages, and B cells (antigen-presenting cells), display antigen fragments to helper T cells and cytotoxic T cells.

### CONCEPT 43.3

#### Lymphocyte Development



#### CONCEPT 43.3

**Acquired immunity defends against infection of body cells and fluids (pp. 942–948)**

- ▶ Infection of body fluids and infection of body cells are subject to humoral and cell-mediated responses, respectively.
- ▶ **Helper T Cells: A Response to Nearly All Antigens** Helper T cells make CD4, a surface protein that enhances their binding to class II MHC molecule–antigen fragment complexes on antigen-presenting cells. Activated helper T cells secrete different cytokines that stimulate other lymphocytes.
- ▶ **Cytotoxic T Cells: A Response to Infected Cells** Cytotoxic T cells make CD8, a surface protein that enhances their binding to class I MHC molecule–antigen fragment complexes on infected cells and cancerous cells. Activated cytotoxic T cells secrete proteins that initiate destruction of their target cells.
- ▶ **B Cells: A Response to Extracellular Pathogens** The clonal selection of B cells generates antibody-secreting plasma cells, the effector cells of the humoral immune response. The five major antibody classes differ in their distributions and functions within the body. Binding of antibodies to antigens on the surface of pathogens leads to elimination of the microbes by phagocytosis and complement-mediated lysis.
- ▶ **Active and Passive Immunization** Active immunity develops naturally in response to an infection; it also develops artificially by immunization (vaccination). In immunization, a nonpathogenic form of a microbe or part of a microbe elicits an immune response to and immunological memory for that

microbe. 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.

- **Immune Rejection** Certain antigens on red blood cells determine whether a person has type A, B, AB, or O blood. Because antibodies to nonself blood antigens already exist in the body, transfusion with incompatible blood leads to destruction of the transfused cells. MHC molecules are responsible for stimulating the rejection of tissue grafts and organ transplants. The chances of successful transplantation are increased if the donor and recipient MHC tissue types are well matched and if immunosuppressive drugs are given to the recipient. Lymphocytes in bone marrow transplants may cause a graft versus host reaction in recipients.

#### MEDIA

MP3 Tutor The Human Immune System

Activity Immune Responses

### C O N C E P T 43.4

#### Disruptions in immune system function can elicit or exacerbate disease (pp. 948–951)

- **Exaggerated, Self-Directed, and Diminished Immune Responses** In localized allergies, IgE attached to receptors on mast cells induces the cells to release histamine and other mediators that cause vascular changes and allergic symptoms. Loss of normal self-tolerance can lead to autoimmune diseases, such as multiple sclerosis. Inborn immunodeficiencies result from hereditary or congenital defects that interfere with innate, humoral, or cell-mediated defenses. AIDS is an acquired immunodeficiency caused by the human immunodeficiency virus (HIV).
- **Acquired Immune System Evasion by Pathogens** Pathogens use antigenic variation, latency, and direct assault on the immune system to thwart immune responses. HIV infection destroys helper T cells, leaving the patient prone to disease due to deficient humoral and cell-mediated immunity.
- **Cancer and Immunity** Although cancers are more common with immunodeficiencies, it is unclear whether this reflects reduced immune response or an increase in infections that contribute to cancer development through inflammation.

#### MEDIA

Activity HIV Reproductive Cycle

Investigation What Causes Infections in AIDS Patients?

Investigation Why Do AIDS Rates Differ Across the U.S.?

### TESTING YOUR KNOWLEDGE

#### SELF-QUIZ

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. What is a characteristic of early stages of local inflammation?
  - a. anaphylactic shock
  - b. fever
  - c. attack by cytotoxic T cells
  - d. release of histamine
  - e. antibody- and complement-mediated lysis of microbes

3. An epitope associates with which part of an antibody?
  - a. the antibody-binding site
  - 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 antibody tail
4. Which of the following is *not* true about helper T cells?
  - a. They function in cell-mediated and humoral responses.
  - b. They are activated by polysaccharide fragments.
  - c. They bear surface CD4 molecules.
  - d. They are subject to infection by HIV.
  - e. When activated, they secrete cytokines.
5. 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 viruses directly; cytotoxic T cells kill virus-infected cells.
  - c. B cells secrete antibodies against a virus; cytotoxic T cells kill virus-infected cells.
  - d. B cells accomplish the cell-mediated response; cytotoxic T cells accomplish the humoral response.
  - e. B cells respond the first time the invader is present; cytotoxic T cells respond subsequent times.
6. Which of the following results in long-term immunity?
  - a. the passage of maternal antibodies to a developing fetus
  - b. the inflammatory response to a splinter
  - c. the injection of serum from people immune to rabies
  - d. the administration of the chicken pox vaccine
  - e. the passage of maternal antibodies to a nursing infant
7. HIV targets include all of the following except
  - a. macrophages.
  - b. cytotoxic T cells.
  - c. helper T cells.
  - d. cells bearing CD4.
  - e. brain cells.

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.

For Self-Quiz answers, see Appendix A.

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#### EVOLUTION CONNECTION

9. Describe one invertebrate defense mechanism and discuss how it is an evolutionary adaptation retained in vertebrates.

#### SCIENTIFIC INQUIRY

10. To test for tuberculosis in AIDS patients, why wouldn’t you inject purified bacterial antigen and assess signs of immune system reaction several days later?

**Biological Inquiry: A Workbook of Investigative Cases** Explore the immune response to flu pathogens with the case “Pandemic Flu (Past and Possible).”