

Scanning electron micrograph of a macrophage at work. A macrophage (green), a large tissue phagocyte, extends projections to surround and engulf tuberculosis bacteria (purple). After internalizing the bacteria, the macrophage will destroy them by lysosomal enzymes. The macrophage will also present bacterial antigens (protein fragments) on its surface that will activate specific helper lymphocytes, setting in motion events leading to production of antibodies against the tuberculosis bacteria.

12

Body Defenses

CHAPTER AT A GLANCE

- 12.1 Immune System: Targets, Effectors, Components
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Homeostasis Highlights



Humans constantly come into contact with external agents that could be harmful if they entered the body. The most serious are disease-causing microorganisms. If bacteria or viruses do gain entry, the body is equipped with a complex, multifaceted internal defense system—the **immune system**—that provides continual protection against invasion by foreign agents. Furthermore, body surfaces exposed to the external environment, such as the **integumentary system (skin)**, serve as a first line of defense to resist penetration by foreign microorganisms. The immune system also protects against cancer and paves the way for repair of damaged tissues.

The immune system indirectly contributes to homeostasis by helping maintain the health of organs that directly contribute to homeostasis.

12.1 Immune System: Targets, Effectors, Components

Immunity is the body's ability to protect itself by resisting or eliminating potentially harmful foreign invaders (such as bacteria and viruses) or abnormal cells (such as cancer cells). The first line of defense against foreign invaders is the epithelial barriers that surround the outer surface of the body (the skin) and line the body cavities (such as the digestive tract and lungs) that are in contact with the external environment. These epithelial barriers are not part of the immune system. We will discuss their roles in the body's overall defense mechanisms after examining the immune system in detail. As an overview, the following activities are attributable to the immune system, an internal defense system that plays a key role in recognizing and either destroying or neutralizing things that are not "normal self":

1. Defending against invading **pathogens** (disease-producing microorganisms).
2. Removing worn-out cells and tissue damaged by trauma or disease, paving the way for wound healing and tissue repair.
3. Identifying and destroying abnormal cells that have originated in the body. This function, termed *immune surveillance*, is the primary internal-defense mechanism against cancer

Pathogenic bacteria and viruses are the major targets of the immune system.

The primary foreign enemies against which the immune system defends are bacteria and viruses. Comparing their relative sizes, if an average bacterium were the size of a pitcher's mound, a virus would be the size of a baseball. **Bacteria** are nonnucleated, single-celled microorganisms self-equipped with all the machinery essential for their own survival and reproduction. Pathogenic bacteria that invade the body cause tissue damage and produce disease largely by releasing enzymes or toxins that physically injure or functionally disrupt affected cells and organs. The disease-producing power of a pathogen is known as its **virulence**.

In contrast to bacteria, **viruses** are not self-sustaining cellular entities. They consist only of nucleic acids (genetic material—DNA or RNA) enclosed by a protein coat. Because they lack cellular machinery for energy production and protein synthesis, viruses cannot carry out metabolism and reproduce unless they invade a **host cell** (a body cell of the infected individual) and take over the cell's biochemical facilities for their own uses. Not only do viruses sap the host cell's energy resources, but the viral nucleic acids also direct the host cell to synthesize proteins needed for viral replication.

When a virus becomes incorporated into a host cell, the body's own defense mechanisms may destroy the cell because they no longer recognize it as a normal self cell. Other ways in which viruses can lead to cell damage or death are by depleting essential cell components, dictating that the cell produce substances toxic to the cell, or transforming the cell into a cancer cell.

Leukocytes are the effector cells of the immune system.

Leukocytes (white blood cells, or WBCs) and their derivatives, along with a variety of plasma proteins, are responsible for immune defense.

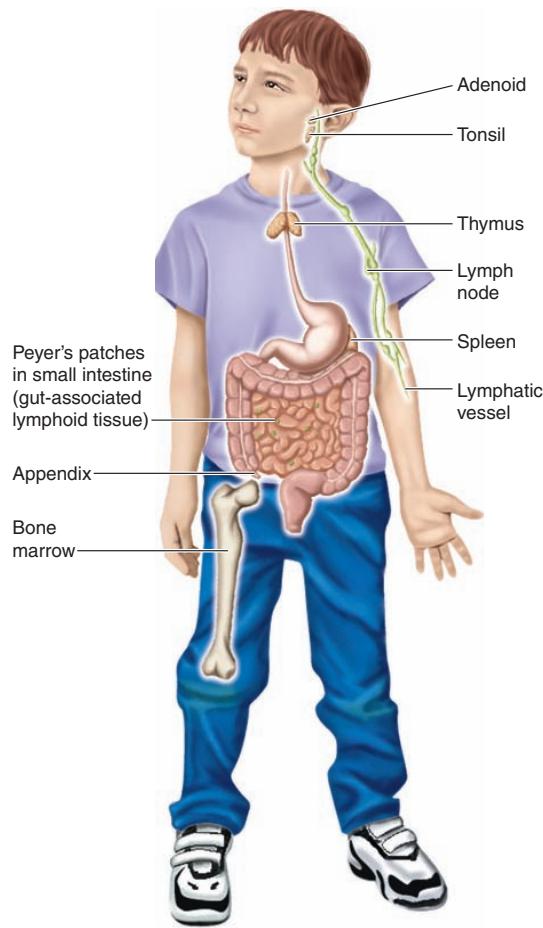
LEUKOCYTE FUNCTIONS As a brief review, the functions of the five types of leukocytes are as follows (see pp. 399 and 402 and ▶ Figures 11-8 and 11-9):

1. **Neutrophils** are highly mobile phagocytic specialists that engulf and destroy unwanted materials.
2. **Eosinophils** secrete chemicals that destroy parasitic worms and are involved in allergic reactions.
3. **Basophils** release histamine and heparin and also are involved in allergic reactions.
4. **Monocytes** are transformed into **macrophages**, which are large, tissue-bound phagocytic specialists.
5. **Lymphocytes** are of two types:
 - a. **B lymphocytes (B cells)** produce antibodies that indirectly lead to the destruction of foreign material (antibody-mediated immunity).
 - b. **T lymphocytes (T cells)** directly destroy virus-invaded cells and mutant cells by releasing chemicals that punch lethal holes in the victim cells (cell-mediated immunity).

A given leukocyte is present in the blood only transiently. Most leukocytes are out in the tissues on defense missions.

LYMPHOID TISSUES Almost all leukocytes originate from common precursor stem cells in the bone marrow and are subsequently released into the blood. The only exception is lymphocytes, which arise in part from lymphocyte colonies in various lymphoid tissues originally populated by cells derived from bone marrow (see p. 403).

Lymphoid tissues, collectively, are the tissues that produce, store, or process lymphocytes. These include the bone marrow, lymph nodes, spleen, thymus, tonsils, adenoids, appendix, and aggregates of lymphoid tissue in the lining of the digestive tract called **Peyer's patches** or **gut-associated lymphoid tissue (GALT)** (▶ Figure 12-1). Lymphoid tissues are strategically located to intercept invading microorganisms before they have a chance to spread very far. For example, lymphocytes populating the *tonsils* and *adenoids* are situated advantageously to respond to inhaled microbes, whereas microorganisms invading through the digestive system immediately encounter lymphocytes in the *appendix* and *GALT*. Potential pathogens that gain access to lymph are filtered through **lymph nodes**, where they are exposed to lymphocytes as well as to macrophages that line lymphatic passageways. The **spleen**, the largest lymphoid tissue, performs immune functions on blood similar to those that lymph nodes perform on lymph. Through actions of its lymphocyte and macrophage population, the spleen clears blood that passes through it of microorganisms and other foreign matter and also removes worn-out red blood cells (see p. 393). The *thymus* and *bone*



► Figure 12-1 Lymphoid tissues. The lymphoid tissues, which are dispersed throughout the body, produce, store, or process lymphocytes.

marrow play important roles in processing T and B lymphocytes, respectively, to prepare them to carry out their specific immune strategies. Table 12-1 summarizes the major functions of the various lymphoid tissues, some described in Chapter 11 and others of which are discussed later in this chapter.

We now turn attention to the two major components of the immune system's response to foreign invaders and other targets—innate and adaptive immune responses. In the process, we will further examine the roles of each type of leukocyte.

Immune responses may be either innate and nonspecific or adaptive and specific.

Protective immunity is conferred by the complementary actions of two separate but interdependent components of the immune system: the innate immune system and the adaptive, or acquired, immune system. The responses of these two systems differ in timing and in the selectivity of the defense mechanisms.

The **innate immune system** encompasses the body's *nonspecific* immune responses that come into play immediately on

► TABLE 12-1 Functions of Lymphoid Tissues

Lymphoid Tissue	Functions
Bone marrow	Origin of all blood cells Site of maturational processing for B lymphocytes
Lymph nodes, tonsils, adenoids, appendix, gut-associated lymphoid tissue	Exchange lymphocytes with the lymph (remove, store, produce, and add them) Resident lymphocytes produce antibodies and activated T cells, which are released into the lymph Resident macrophages remove microbes and other particulate debris from the lymph
Spleen	Exchanges lymphocytes with the blood (removes, stores, produces, and adds them) Resident lymphocytes produce antibodies and activated T cells, which are released into the blood Resident macrophages remove microbes and other particulate debris, most notably worn-out red blood cells, from the blood Stores a small percentage of red blood cells, which can be added to the blood by splenic contraction as needed
Thymus	Site of maturational processing for T lymphocytes Secretes the hormone thymosin

exposure to a threatening agent. These nonspecific responses are inherent (innate or built-in) defense mechanisms that non-selectively defend against foreign or abnormal material of any type, even on initial exposure to it. Such responses provide a first line of internal defense against a range of threats, including infectious agents, chemical irritants, and tissue injury from trauma and burns. Everyone is born with essentially the same innate immune-response mechanisms, although there are some subtle genetic differences. The **adaptive, or acquired, immune system**, in contrast, relies on *specific* immune responses selectively targeted against a particular foreign material to which the body has already been exposed and has had an opportunity to prepare for an attack aimed discriminately at the enemy. The adaptive immune system thus takes considerably more time to mount and takes on specific foes. The innate and adaptive immune systems work in harmony to contain, and then eliminate, harmful agents.

INNATE IMMUNE SYSTEM The components of the innate system are always on guard, ready to unleash a limited repertoire of defense mechanisms at any and every invader. Of the immune effector cells, the neutrophils and macrophages—both phagocytic specialists—are especially important in innate defense. Several groups of plasma proteins also play key roles, as you will see shortly.

The various nonspecific immune responses are set in motion in response to generic molecular patterns associated with threatening agents. Two categories of patterns call forth the innate response: exogenous (originating from outside the body) **pathogen-associated molecular patterns (PAMPs)**, such as the carbohydrates typically found in bacterial cell walls but not found in human cells, and endogenous (originating from within the body) **damage-associated molecular patterns (DAMPs)**, such as extracellular adenosine triphosphate (ATP) released from trauma-damaged cells. Both patterns trigger identical innate pathways leading to inflammation, a multistep process involving phagocytic removal of offending agents and tissue debris and promoting tissue repair. In addition, the response to PAMPs includes augmenting adaptive immunity. We will focus on the response called forth by PAMPs. The responding phagocytic cells possess *pattern recognition receptors* on their surface membrane or in their cytosol for detecting the patterns associated with threatening agents. For example, phagocytes are studded with plasma membrane proteins known as **toll-like receptors (TLRs)**, which recognize PAMPs (and DAMPs). There are about a dozen different TLRs, each of which recognizes a different specific set of molecular patterns. For example, some recognize gram-positive bacteria (bacteria that can be stained with the dark blue Gram stain), others recognize gram-negative bacteria (bacteria whose cell wall does not pick up the Gram stain), still others recognize viral DNA or RNA, and so on. TLRs have been dubbed the “eyes of the innate immune system” because these immune sensors recognize and bind with the unique, telltale pathogen markers, allowing the effector cells of the innate system to “see” pathogens as distinct from normal self cells.

A TLR’s recognition of a pathogen triggers the phagocyte to engulf and destroy the infectious microorganism. Moreover, activation of the TLR induces the phagocytic cell to secrete chemicals, some of which contribute to inflammation. TLRs link the innate and adaptive branches of the immune system because still other chemicals secreted by the phagocytes are important in recruiting cells of the adaptive immune system. Because of their pivotal role in the immune system, TLRs are targets for many new drugs and vaccines under development.

As another link between the innate and adaptive branches of the immune system, foreign particles are deliberately marked for phagocytic ingestion by being coated with antibodies produced by the B cells of the adaptive immune system. These are but a few examples of how various components of the immune system are highly interactive and interdependent. The most significant cooperative relationships among the immune effectors are pointed out throughout this chapter.

TLRs function at the cell surface to recognize pathogens in the extracellular fluid (ECF), but most viruses are hidden inside host cells instead of being free in the ECF. Scientists recently discovered intracellular pattern recognition receptors, such as 3 **retinoic acid inducible gene I (RIG-I)-like receptors (RLRs)**, which recognize viral DNA or RNA within the cytosol, and more than 20 **nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)**, which distinguish intracellular PAMPs such as bits of bacterial cell wall engulfed by a phagocyte or parasites that have invaded a nonimmune cell. Appropriately, activation of RLRs by viral genetic material triggers synthesis of interferon, an innate mechanism to be described later that defends against viral invasion. Activated NLRs trigger formation of cytosolic, multiprotein complexes termed **inflammasomes**, of which the NLRs themselves are a part. Inflammasomes bring about a potent inflammatory response, complementing the actions triggered by activated TLRs. Thus, the trinity of pathogen receptors—TLRs, RLRs, and NLRs—cooperate to ensure efficient innate immune responses against pathogenic interlopers.

The innate mechanisms give us all a rapid but limited and nonselective response to unfriendly challenges of all kinds, much like medieval guardsmen lashing out with brute-force weapons at any enemy approaching the walls of the castle they are defending. Innate immunity largely contains and limits the spread of infection. These nonspecific responses are important for keeping the foe at bay until the adaptive immune system, with its highly selective weapons, can be prepared to take over and mount strategies to eliminate the villain.

ADAPTIVE IMMUNE SYSTEM The responses of the adaptive immune system are mediated by the B and T lymphocytes. Each B and T cell can recognize and defend against only one particular type of foreign material, such as one kind of bacterium. Among the millions of B and T cells in the body, only the ones specifically equipped to recognize the unique molecular features of a particular infectious agent are called into action to discriminantly defend against this agent. This specialization is similar to modern, specially trained military personnel called into active duty to accomplish a specific task. The chosen lymphocytes multiply, expanding the pool of specialists that can launch a highly targeted attack against the invader.

The adaptive immune system is the ultimate weapon against most pathogens. The repertoire of activated and expanded B and T cells is constantly changing in response to the various pathogens encountered. Thus, the adaptive immune system adapts to wage battle against the specific pathogens in each person’s environment. The targets of the adaptive immune system vary among people, depending on the types of immune assaults each individual meets. Furthermore, this system acquires an ability to more efficiently eradicate a particular foe when rechallenged by the same pathogen in the future. It does so by establishing a pool of memory cells as a result of an encounter with a given pathogen so that, when later exposed to the same agent, it can more swiftly defend against the invader.

We examine in more detail the innate immune responses before looking more closely at adaptive immunity.

Check Your Understanding 12.1

1. Define *immunity*.
2. Explain why innate immune responses are considered nonspecific and adaptive immune responses are said to be specific.

12.2 Innate Immunity

Innate defenses include the following:

1. *Inflammation*, a nonspecific response to tissue injury in which the phagocytic specialists—neutrophils and macrophages—play a major role, along with supportive input from other immune cell types
2. *Interferon*, a family of proteins that nonspecifically defend against viral infection
3. *Natural killer cells*, a special class of lymphocyte-like cells that spontaneously and nonspecifically lyse (rupture) and thereby destroy virus-infected host cells and cancer cells
4. The *complement system*, a group of inactive plasma proteins that, when sequentially activated, bring about destruction of foreign cells by attacking their plasma membranes

We discuss each of these in turn, beginning with inflammation.

Inflammation is a nonspecific response to foreign invasion or tissue damage.

The term **inflammation** refers to an innate, nonspecific series of highly interrelated events set into motion in response to foreign invasion, tissue damage, or both. The goal of inflammation is to bring to the invaded or injured area phagocytes and plasma proteins that can (1) isolate, destroy, or inactivate the invaders; (2) remove debris; and (3) prepare for subsequent healing and repair. The overall inflammatory response is remarkably similar no matter what the triggering event (bacterial invasion, chemical injury, or mechanical trauma), although some subtle differences may be evident, depending on the injurious agent or the site of damage. The following sequence of events typically occurs during inflammation. As an example, we use bacterial entry into a break in the skin (► Figure 12-2).

DEFENSE BY RESIDENT TISSUE MACROPHAGES When bacteria invade through a break in the external barrier of skin (or enter through another avenue), macrophages already in the area immediately begin phagocytizing the foreign microbes, defending against infection during the first hour or so, before other mechanisms can be mobilized (see chapter opener photo). Resident macrophages also secrete chemicals such as *chemotaxins* and *cytokines* that exert various immune responses, as will be described shortly (► Figure 12-2, step ①).

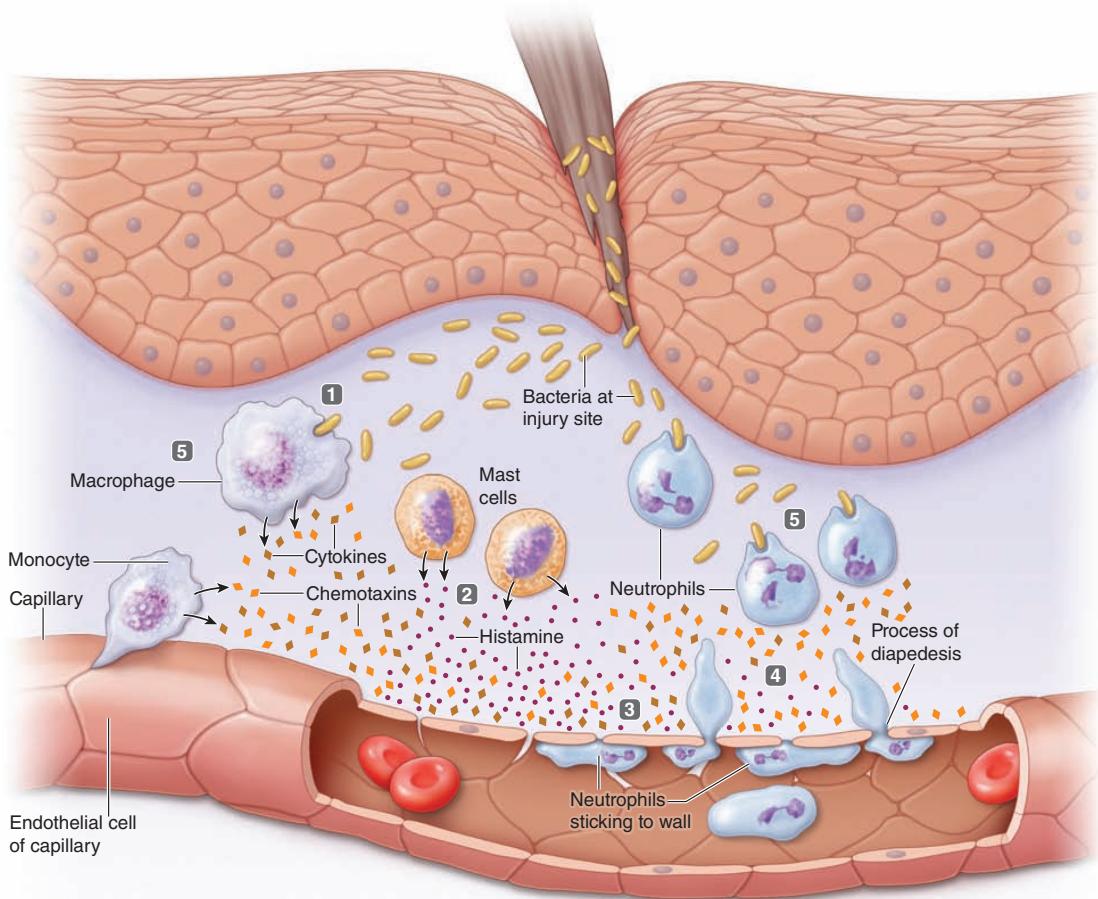
LOCALIZED VASODILATION Almost immediately on microbial invasion, arterioles within the area dilate, increasing blood flow to the site of injury. This localized vasodilation is mainly induced by **histamine** released from mast cells in the area of tissue damage (the connective tissue-bound “cousins” of circulating basophils; see p. 402) (steps ② and ③). Increased local delivery of blood brings to the site more phagocytic leukocytes and plasma proteins, both crucial to the defense response.

INCREASED CAPILLARY PERMEABILITY Released histamine also increases the capillaries' permeability by enlarging the capillary pores (the spaces between the endothelial cells) so that plasma proteins normally prevented from leaving the blood can escape into the inflamed tissue (see p. 364).

LOCALIZED EDEMA Accumulation of leaked plasma proteins in the interstitial fluid raises the local interstitial fluid–colloid osmotic pressure. Furthermore, the increased local blood flow elevates capillary blood pressure. Because both these pressures tend to move fluid out of the capillaries, these changes favor enhanced ultrafiltration and reduced reabsorption of fluid across the involved capillaries. The end result of this shift in fluid balance is localized edema (see p. 366). Thus, the familiar swelling that accompanies inflammation is the result of histamine-induced vascular changes. Likewise, the other well-known gross manifestations of inflammation, such as redness and heat, are largely caused by the enhanced flow of warm arterial blood to the damaged tissue (*inflammare* means “to set on fire”). Pain is caused both by local distension within the swollen tissue and by the direct effect of locally produced substances on the receptor endings of afferent neurons that supply the area. These observable characteristics of the inflammatory process (swelling, redness, heat, and pain) are coincidental to the primary purpose of the vascular changes in the injured area—to increase the number of leukocytic phagocytes and crucial plasma proteins in the area (► Figure 12-3).

WALLING OFF THE INFLAMED AREA The leaked plasma proteins most critical to the immune response are those in the complement system and clotting and anticoagulant factors. On exposure to tissue thromboplastin in the injured tissue and to specific chemicals secreted by phagocytes on the scene, fibrinogen—the final factor in the clotting system—is converted into fibrin (see p. 408). Fibrin forms interstitial fluid clots in the spaces around the bacterial invaders and damaged cells. This walling off of the injured region from the surrounding tissues prevents, or at least delays, the spread of bacterial invaders and their toxic products. Later, the more slowly acting anticoagulant factors gradually dissolve the clots after they are no longer needed (see p. 409).

EMIGRATION OF LEUKOCYTES Within an hour after injury, the area is teeming with leukocytes that have left the vessels. Neutrophils arrive first, followed during the next 8 to 12 hours by the slower-moving monocytes. The latter swell and mature into macrophages during another 8- to 12-hour period. Once neutrophils or monocytes leave the bloodstream, they never recycle back to the blood.



1 A break in the skin introduces bacteria, which reproduce at the wound site. Activated resident macrophages engulf the pathogens and secrete cytokines and chemotaxins.

2 Activated mast cells release histamine.

3 Histamine dilates local blood vessels and widens the capillary pores. The cytokines cause neutrophils and monocytes to stick to the blood vessel wall.

4 Chemotaxins attract neutrophils and monocytes, which squeeze out between cells of the blood vessel wall, a process called diapedesis, and migrate to the infection site.

5 Monocytes enlarge into macrophages. Newly arriving macrophages and neutrophils engulf the pathogens and destroy them.

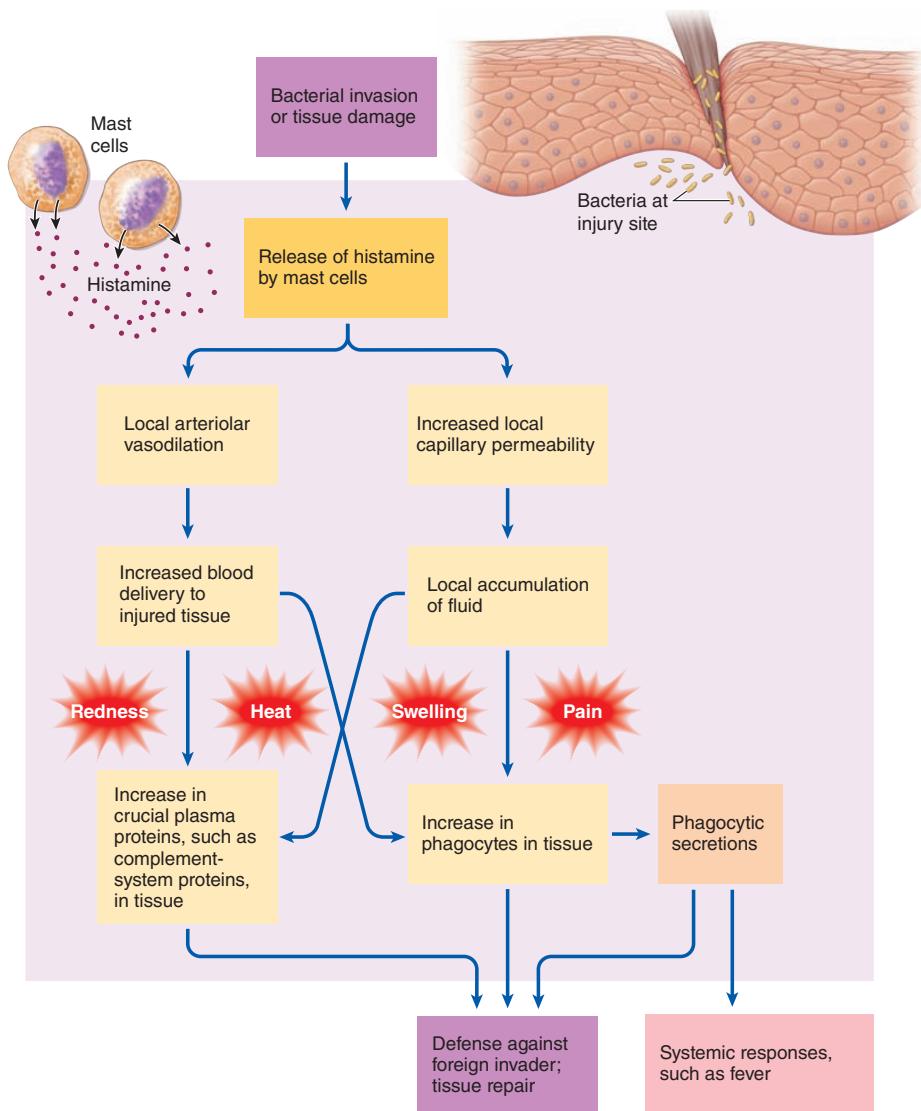
► **Figure 12-2 Steps producing inflammation.** Chemotaxins released at the site of damage attract phagocytes to the scene. Note the leukocytes emigrating from the blood into the tissues by assuming amoeba-like behavior and squeezing through the capillary pores. Mast cells secrete vessel-dilating, pore-widening histamine. Macrophages secrete cytokines that exert multiple local and systemic effects.

Leukocytes can emigrate from the blood into the tissues via the following steps:

- Blood-borne neutrophils and monocytes stick to the inner endothelial lining of capillaries in the affected tissue, a process called **margination** (► Figure 12-2, step **3**). **Selectins**, a type of cell adhesion molecule (CAM; see p. 61) that protrudes from this vessel lining, cause leukocytes flowing by in the blood to slow down and roll along the interior of the vessel, much as the nap of a carpet slows down a child's rolling toy car. This slowing-down allows neutrophils and monocytes enough time to check for local activating factors—"SOS signals", such as

cytokines released by resident microphages in nearby infected tissues. When present, these activating factors cause these leukocytes to adhere firmly to the endothelial lining by means of interaction with another type of CAM, the **integrins**.

- Soon the adhered leukocytes start leaving by a mechanism known as **diapedesis**. Behaving like an amoeba (see p. 51), an adhered leukocyte wriggles through the capillary pore (even though it is much larger than the pore) and then crawls toward the injured area (step **4**). Neutrophils arrive on the inflammatory scene earliest because they are more mobile than monocytes.



► Figure 12-3 Gross manifestations and outcomes of inflammation.

- The phagocytic cells are attracted to **chemotaxins**, chemical mediators released at the site of damage (*taxis* means “attraction”). Binding of chemotaxins with protein receptors on the plasma membrane of a phagocytic cell increases Ca^{2+} entry into the cell. Calcium, in turn, switches on the cellular contractile apparatus that leads to amoeba-like crawling. Because the concentration of chemotaxins progressively increases toward the site of injury, phagocytic cells move unerringly toward this site along a chemotaxin concentration gradient.

LEUKOCYTE PROLIFERATION Resident tissue macrophages and leukocytes that exited from the blood and migrated to the inflammatory site are soon joined by new phagocytic recruits from the bone marrow. Within a few hours after onset of the

inflammatory response, the number of neutrophils in the blood may increase up to four to five times that of normal. A slower-commencing but longer-lasting increase in monocyte production also occurs, making available larger numbers of these macrophage precursor cells (step 5). Mobilization of stored neutrophils and proliferation of new neutrophils, monocytes, and macrophages are stimulated by various chemical mediators (*colony-stimulating factors*; see p. 403) released from the inflamed region.

MARKING OF BACTERIA FOR DESTRUCTION BY OPSO-NINS Phagocytes must be able to distinguish between normal self cells and foreign or abnormal cells before accomplishing their destructive mission. Otherwise, they could not selectively

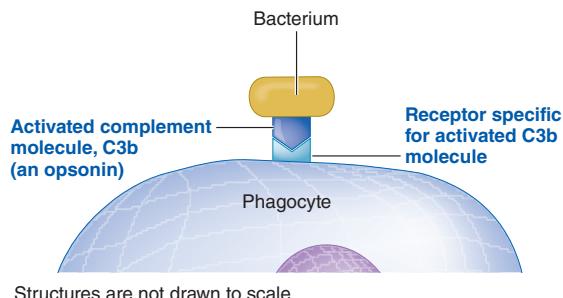
engulf and destroy only unwanted materials. First, phagocytes, by means of their TLRs, recognize and subsequently engulf infiltrators that have standard bacterial cell wall components not found in human cells. Second, foreign particles are deliberately marked for phagocytic ingestion by being coated with chemical mediators generated by the immune system. Such body-produced chemicals that make bacteria more susceptible to phagocytosis are known as **opsonins** (*opsonin* means “to prepare for eating”). The most important opsonins are antibodies and one of the activated proteins of the complement system.

An opsonin enhances phagocytosis by linking the foreign cell to a phagocytic cell (► Figure 12-4). One portion of an opsonin molecule binds nonspecifically to the surface of an invading bacterium, whereas another portion of the opsonin molecule binds to receptor sites specific for it on the phagocytic cell’s plasma membrane. This link ensures that the bacterial victim does not have a chance to “get away” before the phagocyte can perform its lethal attack.

LEUKOCYTIC DESTRUCTION OF BACTERIA Neutrophils and macrophages clear the inflamed area of infectious and toxic agents, and tissue debris, by both phagocytic and nonphagocytic means; this clearing action is the main function of the inflammatory response.

Recall that phagocytosis involves the engulfment of foreign particles and tissue debris, which are degraded intracellularly by hydrolytic enzymes within the confines of lysosomes that fuse with the entrapped material (see p. 32). Macrophages can engulf a bacterium in less than 0.01 second. Phagocytes eventually die from the accumulation of toxic by-products from foreign particle degradation or from inadvertent release of destructive lysosomal chemicals into the cytosol. Neutrophils usually succumb after phagocytizing from 5 to 25 bacteria, whereas macrophages survive much longer and can engulf up to 100 or more bacteria. Indeed, the longer-lived macrophages even clear the area of dead neutrophils in addition to other tissue debris. The **pus** that forms in an infected wound is a collection of these phagocytic cells, both living and dead; necrotic (dead) tissue liquefied by lysosomal enzymes released from the phagocytes; and bacteria.

MEDIATION OF THE INFLAMMATORY RESPONSE BY PHAGOCYTE-SECRETED CHEMICALS Microbe-stimulated phagocytes release many chemicals that function as mediators of inflammation. All chemicals other than antibodies that leukocytes secrete are collectively called **cytokines**. Macrophages, monocytes, neutrophils, a type of T cell called a helper T cell, and some nonimmune cells such as endothelial cells (cells lining blood vessels) and fibroblasts (fiber-formers in the connective tissue) all secrete cytokines. More than 100 cytokines have been identified, and the list continues to grow as researchers unravel the complicated chemical means by which immune effector cells communicate with one another to coordinate their activities. Unlike antibodies, cytokines do not interact directly with the antigen (foreign material) that induces their production. Instead, cytokines largely spur other immune cells into action to help ward off the invader. Cytokines typically act locally as paracrines on cells



► **Figure 12-4 Mechanism of opsonin action.** One of the activated complement molecules, C3b, links a foreign cell, such as a bacterium, and a phagocytic cell by nonspecifically binding with the foreign cell and specifically binding with a receptor on the phagocytic cell. This link ensures that the foreign victim does not escape before it can be engulfed by the phagocyte.

in the vicinity, but some circulate in the blood to exert endocrine effects at distant sites (see p. 117). The cytokines released by phagocytes induce a range of interrelated immune activities, varying from local responses to the systemic manifestations that accompany microbe invasion. Some cytokines have names related to their first identified or most important function, examples being specific *colony-stimulating factors*. Other cytokines are designated as specific numbered *interleukins*, such as interleukin 1 (IL-1), interleukin 2 (IL-2), and so on (*interleukin* means “between leukocytes”); 35 interleukins have been identified to date, numbered in the order of their discovery. Interleukins orchestrate a wide variety of independent and overlapping immune activities. The following are among the most important functions of phagocytic secretions:

1. Some of the chemicals, which are very destructive, directly kill microbes by nonphagocytic means. For example, macrophages secrete *nitric oxide* (NO), a multipurpose chemical that is toxic to nearby microbes (see p. 356). As a more subtle means of destruction, neutrophils secrete **lactoferrin**, a protein that tightly binds with iron, making it unavailable for use by invading bacteria. Bacterial multiplication depends on high concentrations of available iron.
2. Several chemicals released by macrophages, namely **interleukin 1 (IL-1)**, **interleukin 6 (IL-6)**, and **tumor necrosis factor (TNF)** collectively act to bring about a diverse array of effects locally and throughout the body, all of which are geared toward defending the body against infection or tissue injury. They promote inflammation and are largely responsible for the systemic manifestations accompanying an infection. (*Tumor necrosis factor* is named for its role in killing cancer cells, but it also exerts other effects.)
3. The same trio of cytokines function together as **endogenous pyrogen (EP)**, which induces the development of fever (*endogenous* means “from within the body”; *pyro* means “fire” or “heat”; *gen* means “production”). This response occurs especially when the invading organisms have spread into the blood. Endogenous pyrogen causes release within the hypothalamus of **prostaglandins**, locally acting chemical messengers

that “turn up” the hypothalamic “thermostat” that regulates body temperature. The function of the resulting elevation in body temperature in fighting infection remains unclear. Fever is a common systemic manifestation of inflammation, suggesting the raised temperature plays an important beneficial role in the overall inflammatory response, as supported by recent evidence. Higher temperatures appear to augment phagocytosis, increase the rate of the many enzyme-dependent inflammatory activities, and interfere with bacterial multiplication by increasing bacterial requirements for iron. Resolving the controversial issue of whether a fever can be beneficial is extremely important, given the widespread use of drugs that suppress fever.

 Although a mild fever may be beneficial, there is no doubt that an extremely high fever can be detrimental, particularly by harming the central nervous system. Young children, whose temperature-regulating mechanisms are not as stable as those of more mature individuals, occasionally have convulsions in association with high fevers.

4. IL-1, IL-6, and TNF also decrease the plasma concentration of iron by altering iron metabolism within the liver, spleen, and other tissues. This action reduces the amount of iron available to support bacterial multiplication.

5. Furthermore, the same three cytokines stimulate release of **acute phase proteins** from the liver. This collection of proteins, which have not yet been sorted out by scientists, exerts a multitude of wide-ranging effects associated with the inflammatory process, tissue repair, and immune cell activities. One of the better-known acute phase proteins is **C-reactive protein**, considered clinically as a blood-borne marker of inflammation (see p. 337). C-reactive protein serves as a nonspecific opsonin that binds to the surface of many kinds of bacteria.

6. TNF stimulates release of histamine from mast cells in the vicinity. Histamine, in turn, promotes the local vasodilation and increased capillary permeability of inflammation.

7. IL-1 enhances the proliferation and differentiation of both B and T lymphocytes, which, in turn, are responsible for antibody production and cell-mediated immunity, respectively.

8. Colony-stimulating factor from macrophages, lymphocytes, endothelial cells, and fibroblasts stimulates the synthesis and release of neutrophils and monocytes by the bone marrow. This effect is especially prominent in response to bacterial infections.

9. Still other phagocytic chemical mediators trigger both the clotting and anticoagulation systems to first enhance the walling-off process and then facilitate gradual dissolution of the fibrin clot after it is no longer needed.

10. A chemical secreted by neutrophils, **kallikrein**, converts specific plasma protein precursors produced by the liver into activated **kinins**. Activated kinins augment a variety of inflammatory events. For example, the end product of the kinin cascade, **bradykinin**, activates nearby pain receptors and thus partially produces the soreness associated with inflammation. Bradykinin also dilates blood vessels in the area, reinforcing

the effects of histamine. In positive-feedback fashion, kinins also act as powerful chemotaxins to entice more neutrophils to join the battle.

This list of events augmented by phagocyte-secreted chemicals is not complete, but it illustrates the diversity and complexity of responses these mediators elicit. Furthermore, other important macrophage-lymphocyte interactions that do not depend on the release of chemicals from phagocytic cells are described later. Thus, the effect that phagocytes, especially macrophages, ultimately have on microbial invaders far exceeds their “engulf and destroy” tactics.

TISSUE REPAIR The ultimate purpose of the inflammatory process is to isolate and destroy injurious agents and to clear the area for tissue repair. In some tissues (for example, skin, bone, and liver), the healthy organ-specific cells surrounding the injured area undergo cell division to replace the lost cells, often repairing the wound perfectly. In typically nonregenerative tissues such as nerve and muscle, however, lost cells are replaced by **scar tissue**. Fibroblasts, a type of connective tissue cell, start to divide rapidly in the vicinity and secrete large quantities of the protein collagen, which fills in the region vacated by the lost cells and results in the formation of scar tissue (see p. 62). Even in a tissue as readily replaceable as skin, scars sometimes form when complex underlying structures, such as hair follicles and sweat glands, are permanently destroyed by deep wounds.

Inflammation is an underlying culprit in many common, chronic illnesses.

 Acute (short-term) inflammatory responses serve a useful purpose for eliminating pathogens from the body, but scientists are increasingly becoming aware that chronic (long-term), low-grade inflammation may be a unifying theory for many chronic diseases. Chronic inflammation occurs when the triggering agent persists long term, either because it is not entirely eliminated or because it is constantly present or continually renewed. Chronic inflammation has an important role in Alzheimer's disease (p. 167), atherosclerosis and coronary artery disease (see p. 335), asthma (see p. 468), rheumatoid arthritis (see p. 430), obesity (see p. 639), diabetes (see p. 714), possibly cancer, and a host of other health problems. Collectively, these conditions are responsible for the majority of morbidity (illness) and mortality (death). Reining in this underlying inflammatory process could have a huge impact on the quality and quantity of life for much of the world's population.

Nonsteroidal anti-inflammatory drugs and glucocorticoids suppress inflammation.

 Many drugs can suppress inflammation; the most commonly used are the **nonsteroidal anti-inflammatory drugs**, or **NSAIDs** (aspirin, ibuprofen, and related compounds) and **glucocorticoids** (drugs similar to the steroid hormone cortisol, which is secreted by the adrenal cortex and ex-

erts anti-inflammatory actions; see p. 695). For example, aspirin interferes with the inflammatory response by decreasing histamine release, thus reducing pain, swelling, and redness. Furthermore, aspirin reduces fever by inhibiting production of prostaglandins, the local mediators of endogenous pyrogen-induced fever.

Glucocorticoids, which are potent anti-inflammatory drugs, suppress almost every aspect of the inflammatory response. In addition, they destroy lymphocytes within lymphoid tissue and reduce antibody production. These therapeutic agents are useful for treating undesirable immune responses, such as allergic reactions (for example, poison ivy rash and asthma) and the inflammation associated with arthritis. However, by suppressing inflammatory and other immune responses that localize and eliminate bacteria, such therapy also reduces the body's ability to resist infection. For this reason, glucocorticoids should be used discriminately.

Other newer, more specialized classes of anti-inflammatory agents have recently appeared on the market, such as drugs that inhibit TNF and are used, for example, in the treatment of rheumatoid arthritis.

Now let us shift from inflammation to interferon, another component of innate immunity.

Interferon transiently inhibits multiplication of viruses in most cells.

Interferon, a group of three related cytokines, is released from virus-infected cells and briefly provides nonspecific resistance to viral infections by transiently interfering with replication of the same or unrelated viruses in other host cells. In fact, interferon was named for its ability to "interfere" with viral replication.

ANTIVIRAL EFFECT OF INTERFERON When a virus invades a cell, the cell synthesizes and secretes interferon in response to being exposed to viral nucleic acid. Once released into the ECM from a virus-infected cell, interferon binds with receptors on the plasma membranes of healthy neighboring cells or even distant cells that it reaches through the blood, signaling these cells to prepare for possible viral attack. Interferon thus acts as a "whistle-blower," forewarning healthy cells of potential viral attack and helping them prepare to resist. Interferon does not have a direct antiviral effect; instead, it triggers the production of virus-blocking enzymes by potential host cells. When interferon binds with these other cells, they synthesize enzymes that can break down viral messenger RNA (see p. 24) and inhibit protein synthesis. Both these processes are essential for viral replication. Although viruses are still able to invade these forewarned cells, the pathogens cannot govern cellular protein synthesis for their own replication (► Figure 12-5).

The newly synthesized inhibitory enzymes remain inactive within the tipped-off potential host cell unless it is actually invaded by a virus, at which time the enzymes are activated by the presence of viral nucleic acid. This activation requirement protects the cell's own messenger RNA and protein-synthesizing machinery from unnecessary inhibition by these enzymes

should viral invasion not occur. Because activation can take place only during a limited time span, this is a short-term defense mechanism.

Interferon is released nonspecifically from any cell infected by any virus and, in turn, can induce temporary self-protective activity against many different viruses in any other cells that it reaches. Thus, it provides a general, rapidly responding defense strategy against viral invasion until more specific but slower-responding immune mechanisms come into play.

In addition to facilitating inhibition of viral replication, interferon reinforces other immune activities. For example, it enhances macrophage phagocytic activity, stimulates production of antibodies, and boosts the power of killer cells.

ANTICANCER EFFECTS OF INTERFERON Interferon exerts anticancer as well as antiviral effects. It markedly enhances the actions of cell-killing cells—the *natural killer cells*, the component of innate immunity we describe next—and a special type of T lymphocyte, *cytotoxic T cells*—which attack and destroy both virus-infected cells and cancer cells. Furthermore, interferon itself slows cell division and suppresses tumor growth.

Natural killer cells destroy virus-infected cells and cancer cells on first exposure to them.

Natural killer (NK) cells are naturally occurring, lymphocyte-like cells that nonspecifically destroy virus-infected cells and cancer cells by releasing chemicals that directly lyse the membranes of such cells on first exposure to them. NK cells recognize general features of virus-infected cells and cancer cells. Their mode of action and major targets are similar to those of cytotoxic T cells, but the latter can fatally attack only the specific types of virus-infected cells and cancer cells to which they have been previously exposed. Furthermore, after exposure cytotoxic T cells require a maturation period before they can launch their lethal assault. NK cells provide an immediate, nonspecific defense against virus-invaded cells and cancer cells before the more specific and abundant cytotoxic T cells become functional. Antibodies produced as part of the adaptive immune response enhance the killing action of NK cells.

The complement system punches holes in microorganisms.

The **complement system** is another defense mechanism brought into play nonspecifically in response to invading organisms. This system can be activated in two ways (► Figure 12-6a):

1. By exposure to particular carbohydrate chains present on the surfaces of microorganisms but not found on human cells, a nonspecific innate immune response known as the **alternate complement pathway**
2. By exposure to antibodies produced against a specific foreign invader, an adaptive immune response known as the **classical complement pathway**

The system derives its name from its ability to "complement" the action of antibodies; it is the primary mechanism

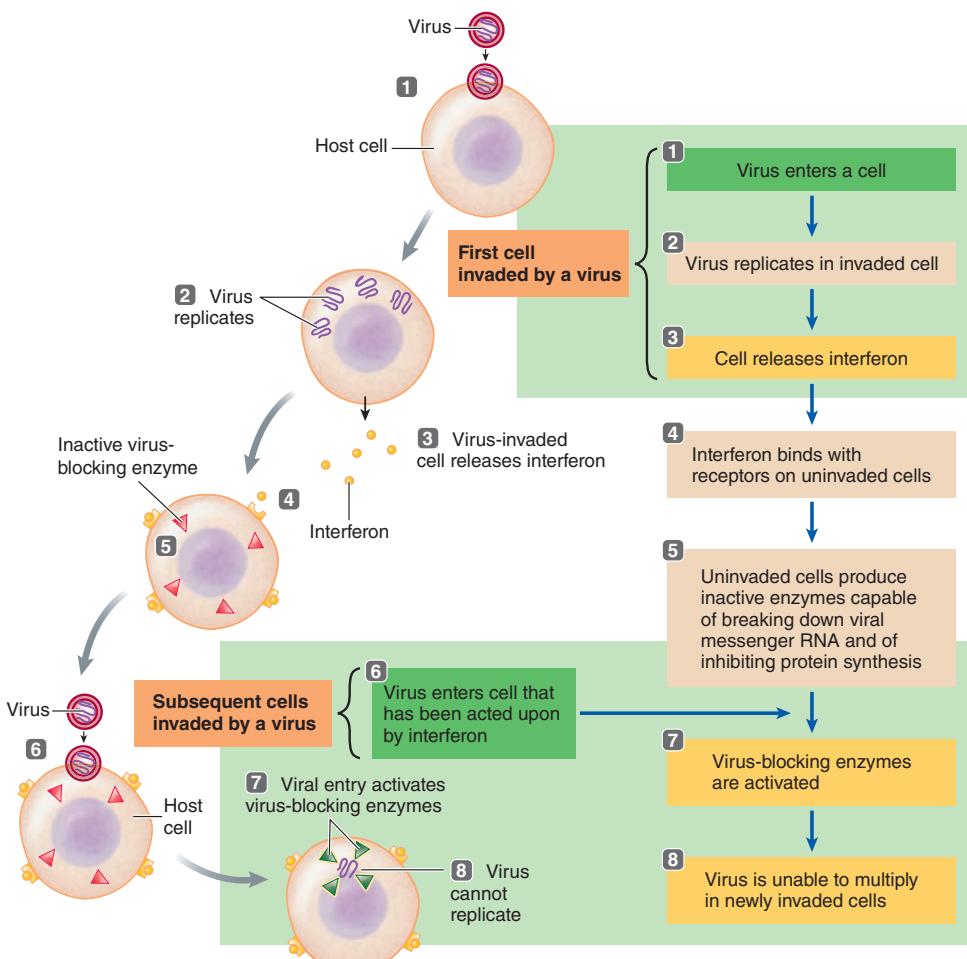


Figure 12-5 Mechanism of action of interferon in preventing viral replication. Interferon, which is released from virus-infected cells, binds with other uninvaded host cells and induces these cells to produce inactive enzymes capable of blocking viral replication. The inactive enzymes are activated only if a virus subsequently invades one of these prepared cells.

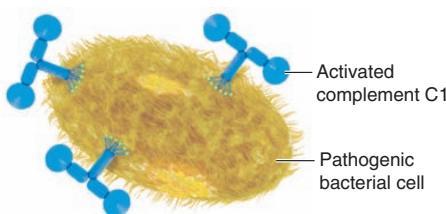
activated by antibodies to kill foreign cells. The complement system destroys cells by forming *membrane attack complexes* that punch holes in the victim cells. In addition to bringing about direct lysis of the invader, the complement cascade reinforces general inflammatory tactics.

FORMATION OF THE MEMBRANE ATTACK COMPLEX In the same mode as the clotting and anticoagulation systems, the complement system consists of an interactive group of more than 30 plasma proteins that are produced by the liver and circulate in the blood in inactive form. Once the first component, C1, is activated, it activates the next component in the sequence, and so on (in the order of C4, C2, C3, then C5 through C9), in a cascade of activation reactions. The five final components, C5 through C9, assemble into a large, doughnut-shaped protein complex, the **membrane attack complex (MAC)**, which embeds itself in the surface membrane of nearby microorganisms, creating a large channel through the membrane (► Figure

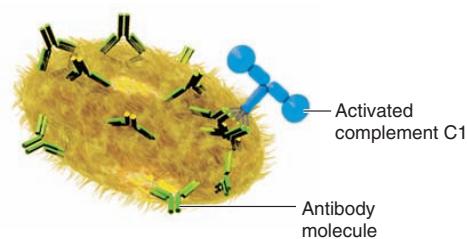
12-6b). In other words, the parts make a hole. This hole-punching technique makes the membrane extremely leaky; the resulting osmotic flux of water into the victim cell causes it to swell and burst. Such complement-induced lysis is the major means of directly killing microbes without phagocytizing them.

AUGMENTING INFLAMMATION Unlike the other cascade systems, in which the sole function of the various components leading up to the end step is activation of the next precursor in the sequence, several activated proteins in the complement cascade additionally act on their own to augment the inflammatory process by the following methods:

- *Serving as chemotaxins*, which attract and guide professional phagocytes to the site of complement activation (that is, the site of microbial invasion)
- *Acting as opsonins* by binding with microbes and thereby enhancing their phagocytosis



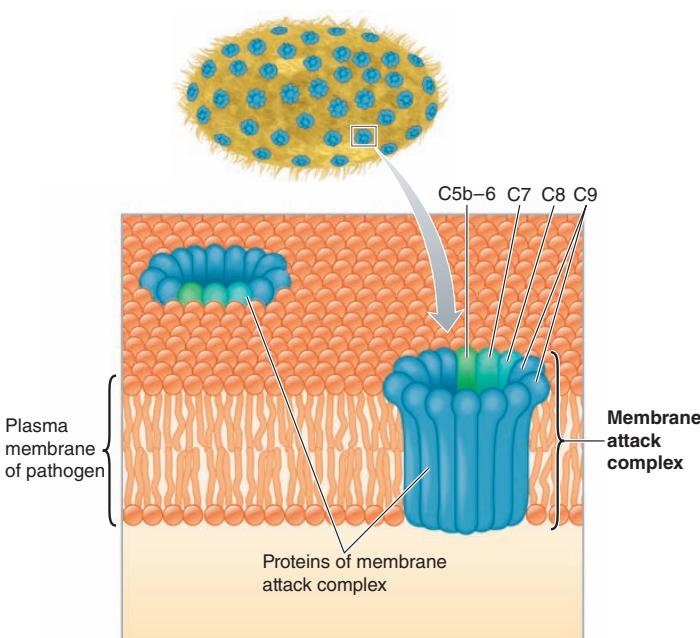
Alternate complement pathway: Binding directly to a foreign invader nonspecifically activates the complement cascade (an innate immune response).



Classical complement pathway: Binding to antibodies (Y-shaped molecules) produced against and attached to a particular foreign invader specifically activates the complement cascade (an adaptive immune response).

(a) Activation of complement system

► **Figure 12-6 Complement system.** (a) Activation of complement system via the alternate pathway and the classical pathway. (b) Formation of membrane attack complex of the complement system.



Activated complement proteins C5, C6, C7, C8, and a number of C9s aggregate to form a porelike channel in the plasma membrane of the target cell. The resulting leakage leads to destruction of the cell.

(b) Formation of membrane attack complex

- Promoting vasodilation and increased vascular permeability, thus increasing blood flow to the invaded area
- Stimulating release of histamine from mast cells in the vicinity, which in turn enhances the local vascular changes characteristic of inflammation
- Activating kinins, which further reinforce inflammatory reactions

Several activated components in the cascade are very unstable, being able to activate the next component in the sequence for less than 0.1 millisecond before assuming an inactive form. Because these unstable components can carry out the sequence only in the immediate area in which they are activated before they decompose, the complement attack is confined to the surface membrane of the microbe whose presence initiated activation of the system. Nearby host cells are thus spared from lytic attack.

We have now completed our discussion of innate immunity and turn our attention to adaptive immunity.

Check Your Understanding 12.2

1. List and briefly describe the four types of innate defense.
2. Define cytokines.

12.3 | Adaptive Immunity: General Concepts

A specific adaptive immune response is a selective attack aimed at limiting or destroying a particular offending target for which the body has been specially prepared after exposure to it.

Adaptive immune responses include antibody-mediated immunity and cell-mediated immunity.

There are two classes of adaptive immune responses: **antibody-mediated**, or **humoral immunity**, involving production of antibodies by B lymphocyte derivatives known as *plasma cells*, and **cell-mediated immunity**, involving production of *activated T lymphocytes*, which directly attack unwanted cells. Because antibodies are blood borne, antibody-mediated immunity is sometimes known as humoral immunity, in reference to the ancient Greek use of the term *humors* for the various body fluids (see p. 347).

Lymphocytes can specifically recognize and selectively respond to an almost limitless variety of foreign agents, as well as cancer cells. The recognition and response processes are different in B and in T cells. In general, B cells recognize free-existing foreign invaders such as bacteria and their toxins and a few

viruses, which they combat by secreting antibodies specific for the invaders. T cells specialize in recognizing and destroying body cells gone awry, including virus-infected cells and cancer cells. We examine each of these processes in detail in the upcoming sections. For now, we explore the different life histories of B and T cells.

ORIGINS OF B AND T CELLS Both types of lymphocytes, like all blood cells, are derived from common stem cells in the bone marrow (see p. 403). Whether a lymphocyte and all its progeny are destined to be B or T cells depends on the site of final differentiation and maturation of the original cell in the lineage (► Figure 12-7). B cells differentiate and mature in the bone marrow. As for T cells, during fetal life and early childhood, some immature lymphocytes from the bone marrow migrate through the blood to the thymus, where they undergo further processing to become T lymphocytes (named for their site of maturation). The **thymus** is a lymphoid tissue located midline within the chest cavity above the heart in the space between the lungs (see ► Figure 12-1, p. 416).

On being released into the blood from either the bone marrow or the thymus, mature B and T cells take up residence and establish lymphocyte colonies in the peripheral lymphoid tissues. Here, on appropriate stimulation, they undergo cell division to produce new generations of either B or T cells, depending on their ancestry. After early childhood, most new lymphocytes are derived from these peripheral lymphocyte colonies rather than from the bone marrow.

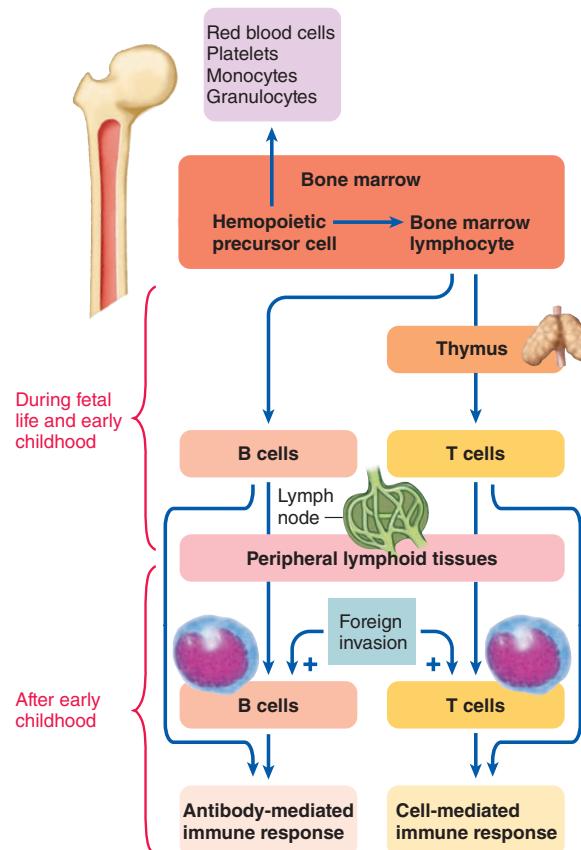
Each of us has an estimated 2 trillion lymphocytes, which, if aggregated in a mass, would be about the size of the brain. At any one time, most of these lymphocytes are concentrated in the various strategically located lymphoid tissues, but both B and T cells continually circulate among the lymph, blood, and body tissues, where they remain on constant surveillance.

ROLE OF THYMOSIN Because most of the migration and differentiation of T cells occurs early in development, the thymus gradually atrophies and becomes less important as the person matures. It does, however, continue to produce **thymosin**, a hormone important in maintaining the T-cell lineage. Thymosin enhances proliferation of new T cells within the peripheral lymphoid tissues and augments the immune capabilities of existing T cells. Secretion of thymosin decreases after about 30 to 40 years of age. This decline has been suggested as a contributing factor in aging. Scientists further speculate that diminishing T-cell capacity with advancing age may be linked to increased susceptibility to viral infections and cancer because T cells play an especially important role in defense against viruses and cancer.

Let us now see how lymphocytes detect their selected target.

An antigen induces an immune response against itself.

Both B and T cells must be able to specifically recognize unwanted cells and other material to be destroyed as being distinct from the body's own normal cells. The presence of anti-



► Figure 12-7 Origins of B and T cells. B cells are derived from lymphocytes that matured and differentiated in the bone marrow, whereas T cells are derived from lymphocytes that originated in the bone marrow but matured and differentiated in the thymus. After early childhood, new B and T cells are produced primarily by colonies of B and T cells established in peripheral lymphoid tissues during fetal life and early childhood.

gens enables lymphocytes to make this distinction. Recall that an **antigen** is a large, unique molecule that triggers a specific immune response against itself, such as generation of antibodies that lead to its destruction, when it gains entry into the body (*antigen* means *antibody generator*, although some antigens trigger cell-mediated immune responses instead of antibody production). In general, the more complex a molecule is, the greater its antigenicity. Foreign proteins are the most common antigens because of their size and structural complexity, although other macromolecules, such as large polysaccharides (carbohydrates) and lipids (fats), can also act as antigens. Antigens may exist as isolated molecules, such as bacterial toxins, or they may be an integral part of a multimolecular structure, as when they are on the surface of an invading foreign microbe.

We first see how B cells respond to their targeted antigen, after which we look at T cells' response to their antigen.

Check Your Understanding 12.3

1. State the two classes of adaptive immunity and indicate which type of lymphocyte accomplishes each.
2. Define antigen.

12.4 | B Lymphocytes: Antibody-Mediated Immunity

Each B and T cell has receptors—**B-cell receptors (BCRs)** and **T-cell receptors (TCRs)**—on its surface for binding with one particular type of the multitude of possible antigens (► Figure 12-8). These receptors are the “eyes of the adaptive immune system,” although a given lymphocyte can “see” only one unique antigen. This is in contrast to the TLRs of the innate effector cells, which recognize generic “trademarks” found on the surface of all microbial invaders.

The antigens to which B cells respond can be T-independent or T-dependent.

B cells can bind with and be directly activated by polysaccharide antigens without any assistance from T cells. These antigens, known as **T-independent antigens**, stimulate production of antibody without any T-cell involvement. By contrast, **T-dependent antigens**, which are typically protein antigens, do not directly stimulate the production of antibody without the help of a special type of T cell known as a *helper T cell*. The majority of antigens to which B cells respond are T-dependent antigens. For now we will consider activation of B cells by binding with antigen without regard to whether or not helper T cells must be present. We will discuss how helper T cells are involved in the response of B cells to T-dependent antigens when we consider the different types of T cells later.

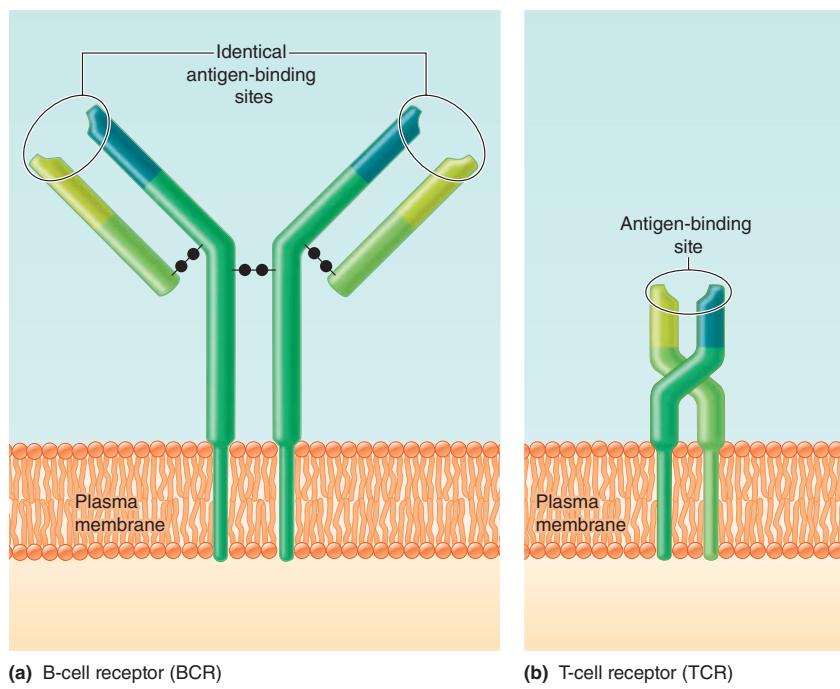
Antigens stimulate B cells to convert into plasma cells that produce antibodies.

When BCRs (► Figure 12-8a) bind with an antigen, most B cells differentiate into active *plasma cells*, whereas others become dormant *memory cells*. We first examine the role of plasma cells and their antibodies and then later in the chapter turn our attention to memory cells.

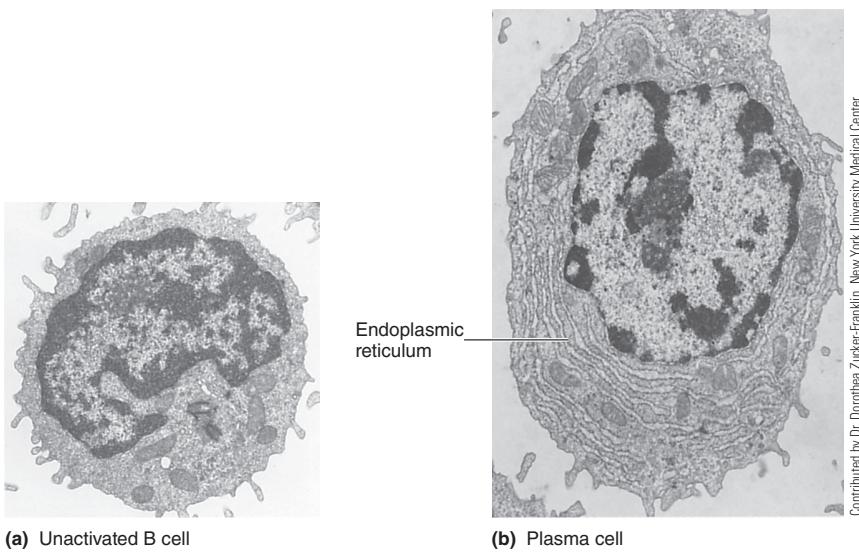
PLASMA CELLS A plasma cell produces **antibodies** that can combine with the specific type of antigen that stimulated activation of the plasma cell. During differentiation into a plasma cell, a B cell swells as the rough endoplasmic reticulum (the site for synthesis of proteins to be exported; see p. 25) greatly expands (► Figure 12-9). Because antibodies are proteins, plasma cells essentially become prolific protein factories, producing up to 2000 antibody molecules per second. So great is the commitment of a plasma cell’s protein-synthesizing machinery to antibody production that it cannot maintain protein synthesis for its own viability and growth. Consequently, it dies after a brief (5- to 7-day), highly productive life span.

ANTIBODY SUBCLASSES Antibodies (also known as *immunoglobulins*; see p. 391) are grouped into five subclasses based on differences in their biological activity:

- **IgM** immunoglobulin serves as the BCR for antigen attachment and is produced in the early stages of plasma cell response.
- **IgG**, the most abundant immunoglobulin in the blood, is produced and secreted copiously when the body is subsequently exposed to the same antigen. IgG antibodies produce most specific immune responses against bacterial invaders.
- **IgE** helps protect against parasitic worms and is the antibody mediator for common allergic responses, such as hay fever, asthma, and hives.
- **IgA** immunoglobulins are found in secretions of the digestive, respiratory, and urogenital (urinary and reproductive) systems and in milk and tears.



► Figure 12-8 B-cell and T-cell receptors.



(a) Unactivated B cell (b) Plasma cell

► **Figure 12-9 Comparison of an unactivated B cell and a plasma cell.** Electron micrographs at the same magnification of (a) an unactivated B cell, or small lymphocyte, and (b) a plasma cell. A plasma cell is an activated B cell. It is filled with an abundance of rough endoplasmic reticulum distended with antibody molecules.

- IgD is present on the surface of many B cells, but its function is unclear.

Note that this classification is based on different ways in which antibodies function. It does not imply that there are only five different antibodies. Within each functional subclass are millions of different antibodies, each able to bind only with a specific antigen.

Antibodies are Y shaped and classified according to properties of their tail portion.

Antibodies of all five subclasses are composed of four inter-linked polypeptide chains—two long, heavy chains and two short, light chains—arranged in the shape of a Y (► Figure 12-10). Characteristics of the arm regions of the Y determine the *specificity* of the antibody (that is, with what antigen the antibody can bind). Properties of the tail portion of the antibody determine the *functional properties* of the antibody (what the antibody does once it binds with an antigen).

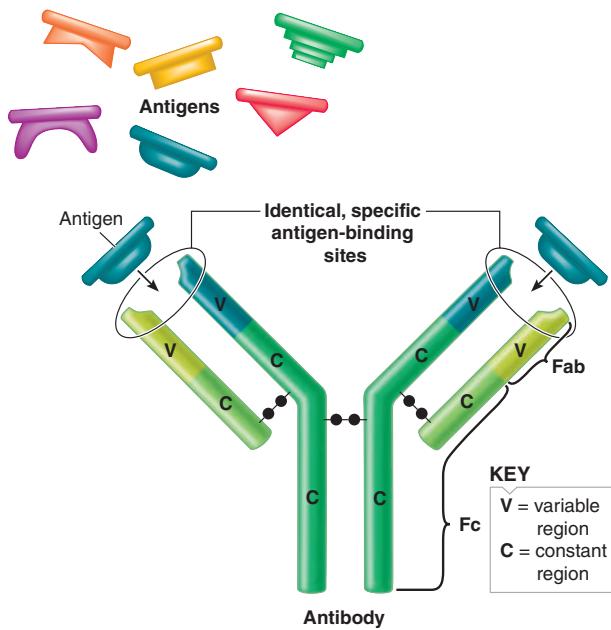
An antibody has two identical antigen-binding sites, one at the tip of each arm. These **antigen-binding fragments** (**Fab**) are unique for each antibody, so each antibody can interact only with an antigen that specifically matches it, much like a lock and key. The tremendous variation in the antigen-binding fragments of different antibodies leads to the extremely large number of unique antibodies that can bind specifically with millions of different antigens.

In contrast to these variable Fab regions at the arm tips, the tail portion of every antibody within each immunoglobulin subclass is identical. The tail, the antibody's **constant (Fc) region**, contains binding sites for particular mediators of antibody-induced activities, which vary among the subclasses. In fact, differences in the

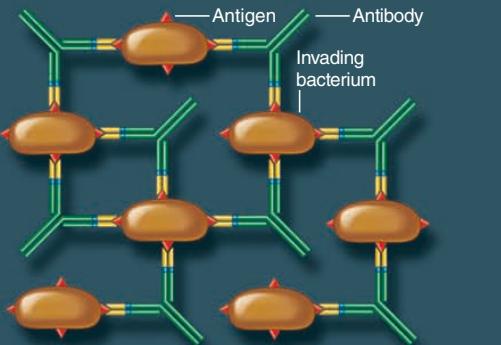
constant region are the basis for distinguishing among the immunoglobulin subclasses. For example, the constant tail region of IgG antibodies, when activated by antigen binding in the Fab region, binds with phagocytic cells and serves as an opsonin to enhance phagocytosis. In comparison, the constant tail region of IgE antibodies attaches to mast cells and basophils, even in the absence of antigens. When the appropriate antigen gains entry to the body and binds with the attached antibodies, this triggers the release of histamine from the affected mast cells and basophils. Histamine, in turn, induces the allergic manifestations that follow.

Antibodies largely amplify innate immune responses to promote antigen destruction.

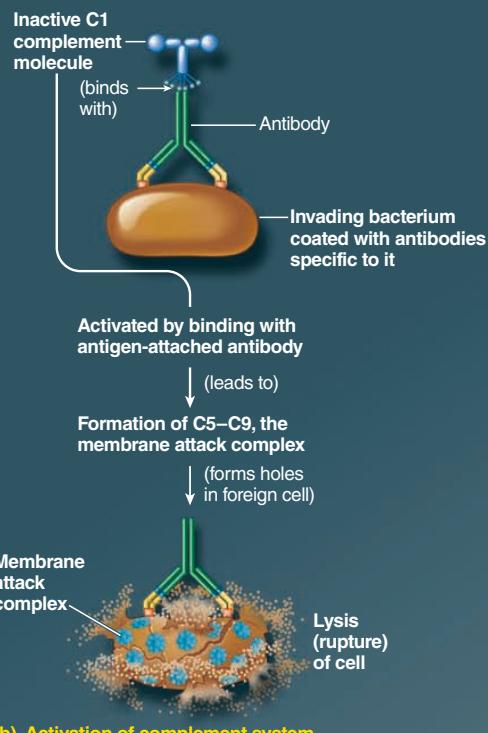
Antibodies cannot directly destroy foreign organisms or other unwanted materials on binding with antigens on their surfaces. Instead, they exert their protective influence by physically hindering antigens or, more commonly, by amplifying innate immune responses.



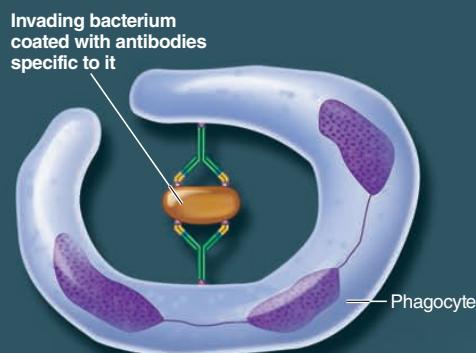
► **Figure 12-10 Antibody structure.** An antibody is Y-shaped. It is able to bind only with the specific antigen that "fits" its antigen-binding sites (Fab) on the arm tips. The tail region (Fc) binds with particular mediators of antibody-induced activities.



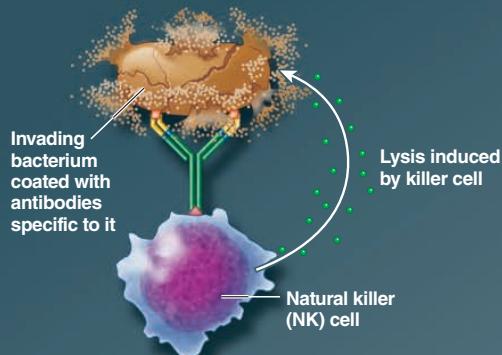
(a) **Agglutination** (clumping of antigenic cells) and **precipitation** (if soluble antigen–antibody complex is too large to stay in solution)



(b) **Activation of complement system**



(c) **Enhancement of phagocytosis (opsonization)**



(d) **Stimulation of natural killer (NK) cells:**
antibody-dependent cellular cytotoxicity

Structures are not drawn to scale.

► **Figure 12-11 How antibodies help eliminate invading microbes.** Antibodies may physically hinder antigens, such as through neutralization or (a) agglutination and precipitation. More commonly, antibodies amplify innate immune responses by (b) activating the complement system, (c) enhancing phagocytosis by acting as opsonins, and (d) stimulating natural killer cells.

PHYSICAL HINDRANCE OF AN ANTIGEN Through neutralization and agglutination, antibodies can physically hinder some antigens from exerting their detrimental effects.

- In **neutralization**, antibodies combine with bacterial toxins, preventing these harmful chemicals from interacting with susceptible cells. Similarly, antibodies can neutralize some types of viruses by binding with their surface antigens and preventing these viruses from entering cells, where they could exert their damaging effects.

- In **agglutination**, multiple antibody molecules cross-link numerous antigen molecules into chains or lattices of antigen–antibody complexes (► Figure 12-11a). Through this means, foreign cells, such as bacteria or mismatched transfused red blood cells, bind together in a clump (see p. 398). When linked antigen–antibody complexes involve soluble antigens, such as tetanus toxin, the lattice can become so large that it precipitates out of solution. (**Precipitation** is the process in which a substance separates from a solution.)

Within the body, these physical hindrance mechanisms play only a minor protective role against invading agents.



However, the tendency for certain antigens to agglutinate or precipitate on forming large complexes with antibodies specific for them is useful for detecting the presence of particular antigens or antibodies. Pregnancy diagnosis tests, for example, use this principle to detect, in urine, the presence of a hormone secreted soon after conception.

AMPLIFICATION OF INNATE IMMUNE RESPONSES The most important function of antibodies by far is to profoundly augment the innate immune responses already initiated by the invaders. Antibodies mark foreign material as targets for actual destruction by the complement system, phagocytes, or NK cells while enhancing the activity of these other defense systems by the following methods:

1. *Activating the complement system.* When an appropriate antigen binds with an antibody, receptors on the tail portion of the antibody bind with and activate C1, the first component of the complement system. This sets off the cascade of events leading to formation of the membrane attack complex, which is specifically directed at the membrane of the invading cell that bears the antigen that initiated the activation process (► Figure 12-11b). Antibodies are the most powerful activators of the complement system (the classical complement pathway). The biochemical attack subsequently unleashed against the invader's membrane is the most important mechanism by which antibodies exert their protective influence. Furthermore, various activated complement components enhance virtually every aspect of the inflammatory process. The same complement system is activated by an antigen–antibody complex regardless of the type of antigen. Although the binding of antigen to antibody is highly specific, the outcome, which is determined by the antibody's constant tail region, is identical for all activated antibodies within a given subclass; for example, all IgG antibodies activate the same complement system.
2. *Enhancing phagocytosis.* Antibodies, especially IgG, act as opsonins. The tail portion of an antigen-bound IgG antibody binds with a receptor on the surface of a phagocyte and subsequently promotes phagocytosis of the antigen-containing victim attached to the antibody (► Figure 12-11c).
3. *Stimulating NK cells.* The binding of antibody to antigen also induces attack of the antigen-bearing target cell by NK cells. NK cells have receptors for the constant tail portion of antibodies. In this case, when the target cell is coated with antibodies, the tail portions of the antibodies link the target cell to NK cells, which destroy the target cell by lysing its plasma membrane (► Figure 12-11d). This process is known as **antibody-dependent cellular cytotoxicity (ADCC)**.

In these ways, antibodies, although unable to directly destroy invading bacteria or other undesirable material, bring about destruction of the antigens to which they are specifically attached, by amplifying other nonspecific lethal defense mechanisms.



IMMUNE COMPLEX DISEASE Occasionally, an overzealous antigen–antibody response inadvertently causes damage to normal cells, as well as to invading foreign

cells. Typically, antigen–antibody complexes, formed in response to foreign invasion, are removed by phagocytic cells after having revved up nonspecific defense strategies. If large numbers of these complexes are continuously produced, however, the phagocytes cannot clear away all the immune complexes formed. Antigen–antibody complexes that are not removed continue to activate the complement system, among other things. Excessive amounts of activated complement and other inflammatory agents may "spill over," damaging the surrounding normal cells, as well as the unwanted cells. Furthermore, destruction is not necessarily restricted to the initial site of inflammation. Antigen–antibody complexes may circulate freely and become trapped in the kidneys, joints, brain, small vessels of the skin, and elsewhere, causing widespread inflammation and tissue damage. Such damage produced by immune complexes is referred to as an **immune complex disease**, which can be a complicating outcome of bacterial, viral, or parasitic infection.

More insidiously, immune complex disease can stem from overzealous inflammatory activity prompted by immune complexes formed by "self-antigens" (proteins synthesized by the person's own body) and antibodies erroneously produced against them. *Rheumatoid arthritis* develops in this way.

Clonal selection accounts for the specificity of antibody production.

Consider the diversity of foreign molecules a person can potentially encounter during a lifetime. Despite this, each B cell is preprogrammed to respond to only 1 of probably more than 100 million different antigens. Other antigens cannot combine with the same B cell and induce it to secrete different antibodies. The astonishing implication is that each of us is equipped with about 100 million kinds of preformed B lymphocytes, at least one B lymphocyte for every possible antigen that we might ever encounter. The **clonal selection theory** proposes how a "matching" B cell responds to its antigen.

Early researchers in immunologic theory believed antibodies were "made to order" whenever a foreign antigen gained entry to the body. In contrast, the currently accepted **clonal selection theory** proposes that diverse B lymphocytes are produced during fetal development, each capable of synthesizing an antibody against a particular antigen before ever being exposed to it. All offspring of a particular ancestral B lymphocyte form a family of identical cells, or a **clone**, that is committed to producing the same specific antibody. B cells remain dormant, not actually secreting their particular antibody product nor undergoing rapid division until (or unless) they come into contact with the appropriate antigen. Lymphocytes that have not yet been exposed to their specific antigen are known as **naive lymphocytes**. When an antigen gains entry to the body, the particular clone of B cells that bear receptors (BCRs) on their surface uniquely specific for that antigen is activated or "selected" by the antigen binding with the BCRs, hence the term **clonal selection theory** (► Figure 12-12).

The first antibodies produced by a newly formed B cell are IgM immunoglobulins, which are inserted into the cell's plasma

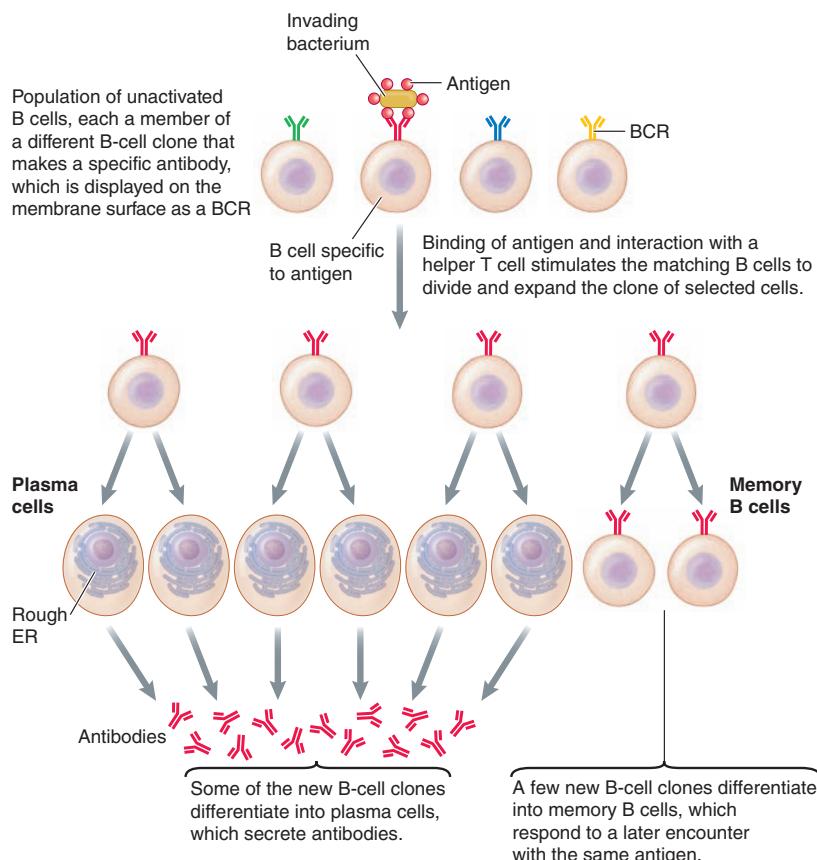


Figure 12-12 Clonal selection theory. The B-cell clone specific to the antigen proliferates and differentiates into plasma cells and memory cells. Plasma cells secrete antibodies that bind with free antigen not attached to B cells. Memory cells are primed and ready for subsequent exposure to the same antigen.

membrane rather than secreted. Here they serve as BCRs for binding with a specific kind of antigen, almost like “advertisements” for the kind of antibody that the cell can produce. Binding of the appropriate antigen to a B cell amounts to “placing an order” for the manufacture and secretion of large quantities of that particular antibody.

Selected clones differentiate into active plasma cells and dormant memory cells.

Antigen binding causes the activated B-cell clone to multiply (the clone expands at the rate of two to three cell divisions per day) and differentiate into two cell types—the previously described plasma cells and memory cells, which we focus on next. Most progeny are transformed into active plasma cells, which are prolific producers of customized antibodies that contain the same antigen-binding sites as the surface receptors. However, plasma cells switch to producing IgG antibodies, which are secreted rather than remaining membrane bound. In the blood, the secreted antibodies combine with the invading, free (not bound to lymphocytes) antigen, marking it for destruction by the complement system, phagocytic ingestion, or NK cells.

cells are formed and does not reach its peak for a couple of weeks. This response is known as the **primary response** (Figure 12-13a). Meanwhile, symptoms characteristic of the particular microbial invasion persist until either the invader succumbs to the mounting specific immune attack against it or the infected person dies. After reaching the peak, the antibody levels gradually decline over time. If the same antigen ever reappears, the long-lived memory cells launch a more rapid, more potent, and longer-lasting **secondary response** than occurred during the primary response (Figure 12-13b). This swifter, more powerful immune attack is frequently adequate to prevent or minimize overt infection on subsequent exposures to the same microbe, forming the basis of long-term immunity against a specific disease.

Clinical Note
The original antigenic exposure that induces the formation of memory cells can occur through the person either having the disease or being vaccinated. **Vaccination (immunization)** deliberately exposes the person to a pathogen that has been stripped of its disease-inducing capability (that is, the pathogen is *attenuated*) but that can still induce antibody formation against itself. (For the early history of vaccination development, see the boxed feature on p. 432, Concepts, Challenges, and Controversies.)

MEMORY CELLS Not all new B lymphocytes produced by the specifically activated clone differentiate into antibody-secreting plasma cells. A small proportion become **memory cells**, which do not participate in the current immune attack against the antigen but instead remain dormant and expand this specific clone. If the person is ever reexposed to the same antigen, these memory cells are primed and ready for even more immediate activation than the original lymphocytes in the clone were.

Even though each of us has essentially the same original pool of different B-cell clones, the pool gradually becomes appropriately biased to respond most efficiently to each person’s particular antigenic environment. Those clones specific for antigens to which a person is never exposed remain dormant for life, whereas those specific for antigens in the individual’s environment typically become expanded and enhanced by forming highly responsive memory cells. The different naive clones provide protection against unknown new pathogens, and the evolving populations of memory cells protect against the recurrence of infections encountered in the past.

PRIMARY AND SECONDARY RESPONSES

During initial contact with a microbial antigen, the antibody response is delayed for several days until plasma

Vaccination: A Victory over Many Dreaded Diseases

MODERN SOCIETY HAS COME TO HOPE and even expect that vaccines can be developed to protect us from almost any dreaded infectious disease. This expectation has been brought into sharp focus by our current frustration over the inability to date to develop a successful vaccine against HIV, the virus that causes AIDS.

Nearly 2500 years ago, our ancestors were aware of the existence of immune protection. Writing about a plague that struck Athens in 430 bc, Thucydides observed that the same person was never attacked twice by this disease. However, the ancients did not understand the basis of this protection, so they could not manipulate it to their advantage.

Early attempts to deliberately acquire lifelong protection against smallpox, a dreaded disease that was highly infectious and frequently fatal (up to 40% of the sick died), consisted of intentionally exposing oneself by coming into direct contact with a person suffering from a milder form of the disease. The hope was to protect against a future fatal bout of smallpox by deliberately inducing a mild case of the disease. By the beginning of the 17th century, this technique had evolved into using a needle to extract small amounts of pus from active smallpox pustules (the fluid-filled bumps on the skin, which leave a characteristic depressed scar or “pock” mark after healing) and introducing this infectious material into healthy individuals. This inoculation process was done by applying the pus directly to slight cuts in the skin or by inhaling dried pus.

Edward Jenner, an English physician, was the first to demonstrate that immunity against cowpox, a disease similar to but less serious

than smallpox, could also protect humans against smallpox. Having observed that milkmaids who got cowpox seemed to be protected from smallpox, Jenner in 1796 inoculated a healthy boy with pus he had extracted from cowpox boils (*vaccina*, as in *vaccination*, means “cow”). After the boy recovered, Jenner (not being restricted by modern ethical standards of research on human subjects) deliberately inoculated him with what was considered a normally fatal dose of smallpox infectious material. The boy survived.

Jenner’s results were not taken seriously, however, until a century later when, in the 1880s, Louis Pasteur, the first great experimental immunologist, extended Jenner’s technique. Pasteur demonstrated that the disease-inducing capability of organisms could be greatly reduced (attenuated) so that they could no longer produce disease but would still induce antibody formation when introduced into the body—the basic principle of modern vaccines. His first vaccine was against anthrax, a deadly disease of sheep and cows. Pasteur isolated and heated anthrax bacteria and then injected these attenuated organisms into a group of healthy sheep. A few weeks later, at a gathering of fellow scientists, Pasteur injected these vaccinated sheep and a group of unvaccinated sheep with fully potent anthrax bacteria. The result was dramatic—all the vaccinated sheep survived, but all the unvaccinated sheep died. Pasteur’s notorious public demonstrations such as this, coupled with his charismatic personality, caught the attention of physicians and scientists of the time, sparking the development of modern immunology.

Memory cells are not formed for some diseases such as “strep throat,” so lasting immunity is not conferred by an initial exposure. The course and severity of the disease are the same each time a person is reinfected with a microbe that the immune system does not “remember,” regardless of the number of prior exposures.

Active immunity is self-generated; passive immunity is “borrowed.”

The production of antibodies as a result of exposure to an antigen is referred to as **active immunity** against that antigen. A second way in which an individual can acquire antibodies is by direct transfer of antibodies actively formed by another person (or animal). The immediate “borrowed” immunity conferred on receipt of preformed antibodies is known as **passive immunity**. Such transfer of anti-

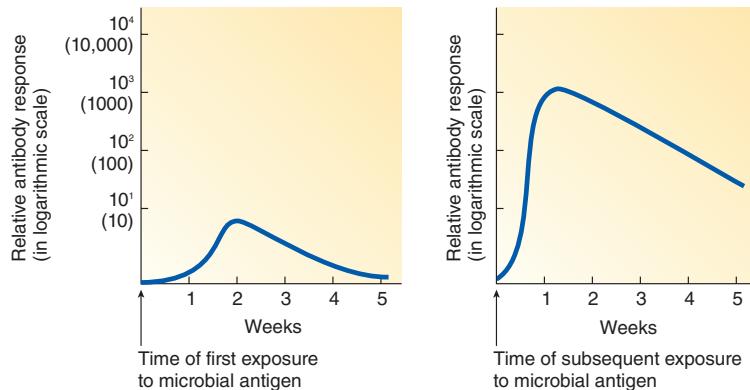


Figure 12-13 Primary and secondary immune responses. (a) Primary response on first exposure to a microbial antigen. (b) Secondary response on subsequent exposure to the same microbial antigen. The primary response does not peak for a couple of weeks, whereas the secondary response peaks in a week. The magnitude of the secondary response is 100 times that of the primary response.

bodies of the IgG class normally occurs from the mother to the fetus across the placenta during intrauterine development. In addition, a mother's colostrum (first milk) contains IgA antibodies that provide further protection for breast-fed babies. Passively transferred antibodies are usually broken down in less than a month, but meanwhile the newborn is provided important immune protection (essentially the same as its mother's) until it can begin actively mounting its own immune responses. Antibody-synthesizing ability does not develop for about a month after birth.

 Passive immunity is sometimes used clinically to provide immediate protection or to bolster resistance against an extremely virulent infectious agent or potentially lethal toxin to which a person has been exposed (for example, rabies virus, tetanus toxin in nonimmunized individuals, and poisonous snake venom). Typically, the administered preformed antibodies have been harvested from another source (often nonhuman) that has been exposed to an attenuated form of the antigen. Frequently, horses or sheep are used in the deliberate production of antibodies to be collected for passive immunizations. Although injection of serum containing these antibodies (**antisera** or **antitoxin**) is beneficial in providing immediate protection against the specific disease or toxin, the recipient may develop an immune response against the injected antibodies themselves because they are foreign proteins. The result may be a severe allergic reaction to the treatment, a condition known as **serum sickness**.

The huge repertoire of B cells is built by reshuffling a small set of gene fragments.

Considering the millions of different antigens against which each of us has the potential to actively produce antibodies, how is it possible for an individual to have such a tremendous diversity of B lymphocytes, each capable of producing a different antibody? Antibodies are proteins synthesized in accordance with a nuclear DNA blueprint. Because all cells of the body, including the antibody-producing cells, contain the same nuclear DNA, it is hard to imagine how enough DNA could be packaged within the nuclei of every cell to code for the 100 million different antibodies (a different portion of the genetic code being used by each B-cell clone), along with all the other genetic instructions used by other cells. Actually, only a relatively small number of gene fragments code for antibody synthesis, but during B-cell development these fragments are cut, reshuffled, and spliced in a vast number of different combinations. Each different combination gives rise to a unique B-cell clone. Antibody genes are later even further diversified by mutations. The antibody genes of already-formed B cells are highly prone to mutations in the region that codes for the variable antigen-binding sites on the antibodies. Each different mutant cell in turn gives rise to a new clone. In this way, a huge antibody repertoire is possible using only a modest share of the genetic blueprint.

We now turn our attention to T cells.

Check Your Understanding 12.4

1. Describe the structure and function of the Fab and Fc regions of an antibody.
2. List the means by which antibodies help eliminate invading microbes.
3. According to the clonal selection theory, draw a flow diagram showing the formation of plasma cells and memory cells in response to the binding of an antigen to its specific B-cell receptor.

12.5 | T Lymphocytes: Cell-Mediated Immunity

As important as B lymphocytes and their antibody products are in specific defense against invading bacteria and other foreign material, they represent only half of the body's specific immune defenses. The T lymphocytes are equally important in defense against most viral infections and also play an important regulatory role in immune mechanisms.

T cells bind directly with their targets.

Whereas B cells and antibodies defend against conspicuous invaders in the ECF, T cells defend against covert invaders that hide inside cells where antibodies and the complement system cannot reach them. Unlike B cells, which secrete antibodies that can attack antigens at long distances, T cells do not secrete antibodies. Instead, they must directly contact their targets, a process known as *cell-mediated immunity*. T cells of the killer type release chemicals that destroy the targeted cells they contact, such as virus-infected cells and cancer cells.

Like B cells, T cells are clonal and exquisitely antigen specific. On its plasma membrane, each T cell bears unique receptor proteins called *T-cell receptors (TCRs)*, similar although not identical to the surface receptors on B cells (see > Figure 12-8b, p. 427). Immature lymphocytes acquire their TCRs in the thymus during their differentiation into T cells. Unlike B cells, T cells are activated by a foreign antigen only when it is on the surface of a cell that also carries a marker of the individual's own identity; that is, both foreign antigens and **self-antigens** known as **major histocompatibility complex (MHC) molecules** must be on a cell's surface before a T cell can bind with it. During thymic education, T cells learn to recognize foreign antigens only in combination with the person's own tissue antigens—a lesson passed on to all T cells' future progeny. The importance of this dual antigen requirement and the nature of the MHC self-antigens are described shortly.

A delay of a few days generally follows exposure to the appropriate antigen before **activated T cells** are prepared to launch a cell-mediated immune attack. When exposed to a specific antigen combination, cells of the complementary T-cell clone proliferate and differentiate for several days, yielding large numbers of activated effector T cells that carry out various cell-mediated responses.

Like B cells, T cells form a memory pool and display both primary and secondary responses. Primary responses tend to be initiated in the lymphoid tissues. During a few-week period after the infection is cleared, more than 90% of the huge number of effector T cells generated during the primary response die by means of *apoptosis* (cell suicide; see p. 42). To stay alive, activated T lymphocytes require the continued presence of their specific antigen and appropriate stimulatory signals. Once the foe succumbs, the vast majority of the now superfluous T lymphocytes commit suicide because their supportive antigen and stimulatory signals are withdrawn. Elimination of most of the effector T cells following a primary response is essential to prevent congestion in the lymphoid tissues. (Such paring down is not needed for B cells—those that become plasma cells and not memory B cells on antigen stimulation rapidly work themselves to death producing antibodies.) The remaining surviving effector T cells become long-lived memory T cells that migrate to all areas of the body, where they are poised for a swift secondary response to the same pathogen in the future.

The three types of T cells are cytotoxic, helper, and regulatory T cells.

The three subpopulations of T cells can be designated in two ways: by their roles when activated by an antigen or by specific proteins associated with their outer membrane. By role, the three types of T cells are *cytotoxic T cells*, *helper T cells*, and *regulatory T cells*. By specific membrane protein type, these same cells are *CD8+ T cells*, *CD4+ T cells*, and *CD4+CD25+ T cells*, respectively. The various types of immune cells have a number of specific immune-related surface membrane proteins given official *cluster designation (CD) numbers* that help characterize them.

■ **Cytotoxic, or killer, T cells** destroy host cells harboring anything foreign and thus bearing a foreign antigen, such as body cells invaded by viruses, cancer cells that have mutated proteins resulting from malignant transformations, and transplanted cells. The T-cell receptors for cytotoxic T cells are associated with **coreceptors** designated CD8, which are inserted into the plasma membrane as these cells pass through the thymus. Therefore, these cells are also known as **CD8+ T cells**.

■ **Helper T cells** do not directly participate in immune destruction of invading pathogens. Instead, they modulate activities of other immune cells. Because of the important role they play in “turning on” the full power of all the other activated lymphocytes and macrophages, helper T cells constitute the immune system’s “master switch.” Helper T cells are by far the most numerous T cells, making up 60% to 80% of circulating T cells. The T-cell receptors for helper T cells are associated with coreceptors designated CD4. Accordingly, helper T cells are also called **CD4+ cells**.

■ **Regulatory T cells (T_{regs})** are a recently identified small subset of CD4+ cells. They have the same CD4 coreceptors as the helper T cells, but in addition they also have CD25, a component of a receptor for IL-2, which promotes T_{reg} activities. Thus, these cells are also referred to as **CD4+CD25+ T cells**.

We now examine the functions of these T cell types in further detail.

Cytotoxic T cells secrete chemicals that destroy target cells.

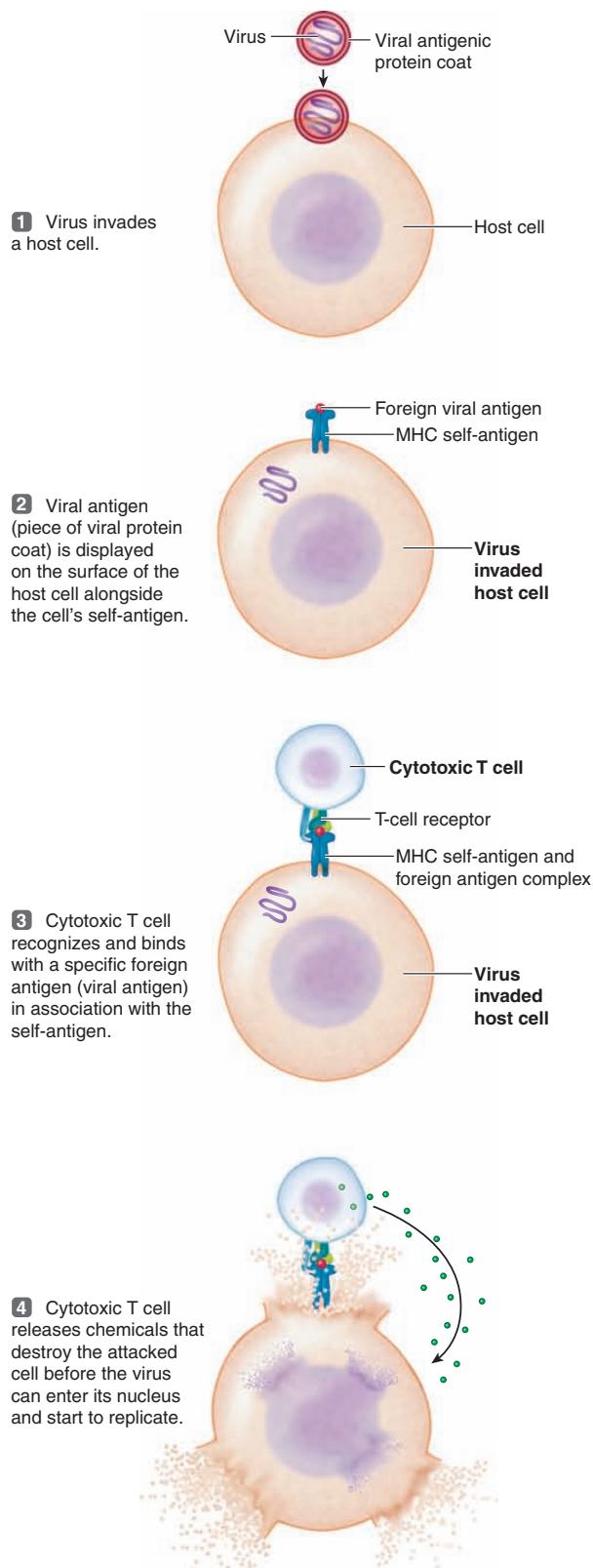
Cytotoxic T cells are microscopic “hit men.” The targets of these destructive cells most frequently are host cells infected with viruses. When a virus invades a body cell, as it must to survive (► Figure 12-14, step 1), the cell breaks down the envelope of proteins surrounding the virus and loads a fragment of this viral antigen piggyback onto a newly synthesized MHC self-antigen. This self-antigen–viral antigen complex is inserted into the host cell’s surface membrane, where it serves as a red flag indicating the cell is harboring the invader (step 2). To attack the intracellular virus, cytotoxic T cells must destroy the infected host cell in the process. Cytotoxic T cells of the clone specific for this particular virus recognize and bind to the viral antigen and self-antigen on the surface of an infected cell (step 3). Thus activated by the viral antigen, a cytotoxic T cell can kill the infected cell by either direct or indirect means, depending on the type of lethal chemicals the activated T cell releases. Let us elaborate.

- An activated cytotoxic T cell may directly kill the victim cell by releasing chemicals that lyse the attacked cell before viral replication can begin (step 4). Specifically, cytotoxic T cells, as well as NK cells, destroy a targeted cell by releasing **perforin** molecules, which penetrate the target cell’s surface membrane and join to form porelike channels (► Figure 12-15). This technique of killing a cell by punching holes in its membrane is similar to the method employed by the membrane attack complex of the complement cascade. This contact-dependent mechanism of killing has been nicknamed the “kiss of death.”
- A cytotoxic T cell can also indirectly bring about death of an infected host cell by releasing **granzymes**, which are enzymes similar to digestive enzymes. Granzymes enter the target cell through the perforin channels. Once inside, these chemicals trigger the virus-infected cell to self-destruct through apoptosis.

The virus released on destruction of the host cell by either of these methods is directly destroyed in the ECF by phagocytic cells, neutralizing antibodies, and the complement system. Meanwhile, the cytotoxic T cell, which has not been harmed in the process, can move on to kill other infected host cells.

The surrounding healthy cells replace the lost cells by means of cell division. Usually, to halt a viral infection, only some of the host cells must be destroyed. If the virus has had a chance to multiply, however, with replicated virus leaving the original cell and spreading to other host cells, the cytotoxic T-cell defense mechanism may sacrifice so many of the host cells that serious malfunction may ensue.

Recall that other nonspecific defense mechanisms come into play to combat viral infections, including macrophages, the complement system, interferon, and NK cells. As usual, an intricate web of interplay exists among the immune defenses that are launched against viral invaders (► Table 12-2).



► Figure 12-14 A cytotoxic T cell lysing a virus-invaded cell.

■ TABLE 12-2 Defenses Against Viral Invasion

When the virus is free in the ECF,

Macrophages

Destroy the free virus by phagocytosis.

Process and present the viral antigen to helper T cells.

Secret IL-1, which activates B- and T-cell clones specific to the viral antigen.

Plasma Cells Derived from B Cells Specific to the Viral Antigen Secrete Antibodies That

Neutralize the virus to prevent its entry into a host cell.

Act as opsonins to enhance phagocytosis of the virus.

Activate the lethal complement cascade as part of adaptive immunity.

The Complement System

Directly destroys the free virus by forming a hole-punching membrane attack complex.

Acts as an opsonin to enhance phagocytosis of the virus.

When the virus has entered a host cell (which it must do to survive and multiply, with the replicated viruses leaving the original host cell to enter the ECF in search of other host cells),

Interferon

Is secreted by virus-infected cells.

Binds with and prevents viral replication in other host cells.

Enhances the killing power of macrophages, natural killer cells, and cytotoxic T cells.

Natural Killer (NK) Cells

Nonspecifically lyse virus-infected host cells.

Cytotoxic T Cells

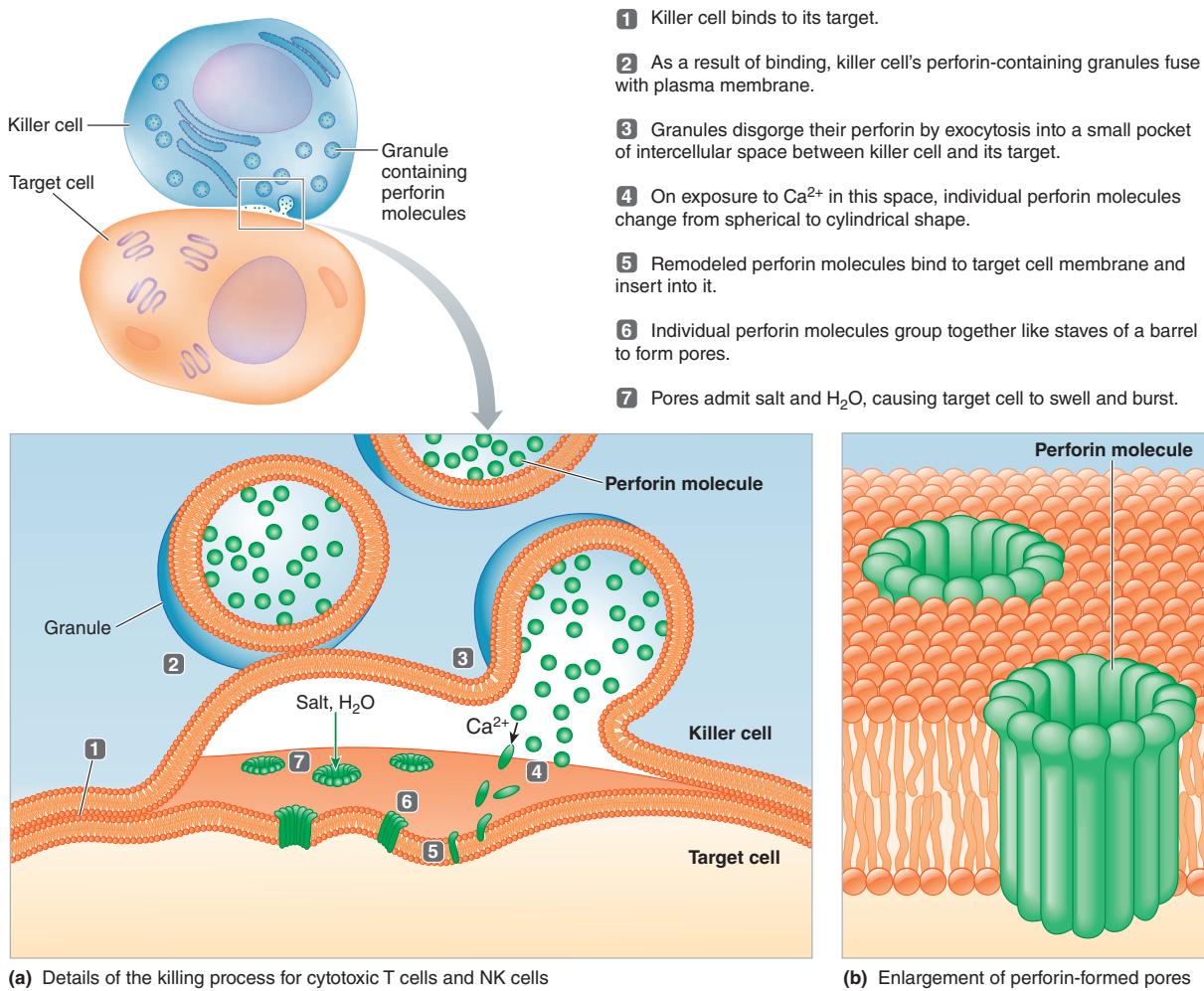
Are specifically activated by the viral antigen and lyse the infected host cells before the virus has a chance to replicate.

Helper T Cells

Secret cytokines, which enhance cytotoxic T-cell activity and B-cell antibody production.

When a virus-infected cell is destroyed, the free virus is released into the ECF, where it is attacked directly by macrophages, antibodies, and the activated complement components.

HYBRID NATURAL KILLER T CELLS A recently discovered subclass of cytotoxic T cells, **natural killer T (NKT) cells**, have properties of both NK cells and cytotoxic T cells. Constituting only 0.2% of all circulating T cells, the hybrid NKT cells have both NK-cell markers and T-cell receptors and thus sit at the crossroads of innate and adaptive immunity. Scientists are



► **Figure 12-15 Mechanism of killing by killer cells.** Note the similarity of the perforin-formed pores in a target cell to the membrane attack complex formed by complement molecules (see ► Figure 12-6b, p. 425).

(Source: Adapted from the illustration by Dana Burns-Pizer in "How Killer Cells Kill," by John Ding-E Young and Zanvil A. Cohn in *Scientific American*, 1988.)

scrambling to identify the physiological roles of these multi-functional cells. Evidence suggests that they are important in suppression of autoimmunity (erroneous production of antibodies against self-antigens) and in tumor rejection.

DEFENSE IN THE NERVOUS SYSTEM The usual method of destroying virus-infected host cells is not appropriate for the nervous system. If cytotoxic T cells destroyed virus-infected neurons, the lost cells could not be replaced because neurons cannot reproduce. Fortunately, virus-infected neurons are spared from extermination by the immune system, but how, then, are neurons protected from viruses? Immunologists long thought that the only antiviral defenses for neurons were those aimed at free viruses in the ECF. Surprising new research has revealed, however, that antibodies not only target viruses for destruction in the ECF but can also eliminate viruses inside neurons. It is unclear whether anti-

bodies actually enter the neurons and interfere directly with viral replication (neurons have been shown to take up antibodies near their synaptic endings) or bind with the surface of nerve cells and trigger intracellular changes that stop viral replication.

Clinical Note The fact that some viruses, such as the herpes virus, persist for years in nerve cells, occasionally "flaring up" to produce symptoms, demonstrates that the antibodies' intraneuronal mechanism does not provide a foolproof antiviral defense for neurons.

Helper T cells secrete chemicals that amplify the activity of other immune cells.

In contrast to cytotoxic T cells, helper T cells are not killer cells. Instead, helper T cells secrete cytokines that "help" or augment, nearly all aspects of the immune response. Most cytokines are

produced by helper T cells. The following are among the best known of helper T-cell cytokines:

1. Helper T cells secrete several interleukins (*IL-4*, *IL-5*, and *IL-6*) that serve collectively as a **B-cell growth factor**, which contributes to B-cell function in concert with the *IL-1* secreted by macrophages. Antibody secretion is greatly reduced or absent without the assistance of helper T cells, especially in defense against T-dependent antigen.
2. Helper T cells similarly secrete **T-cell growth factor** (*IL-2*), which augments the activity of cytotoxic T cells and even of other helper T cells responsive to the invading antigen. In typical interplay fashion, *IL-1* secreted by macrophages not only enhances the activity of both the appropriate B- and T-cell clones but also stimulates secretion of *IL-2* by activated helper T cells.
3. Some chemicals secreted by T cells act as *chemotaxins* to lure more neutrophils and macrophages-to-be to the invaded area. Cytokines that act as chemotaxins are specifically called **chemokines**.
4. Once macrophages are attracted to the area, **macrophage-migration inhibition factor**, another important cytokine released from helper T cells, keeps these large phagocytic cells in the region by inhibiting their outward migration. As a result, many chemotactically attracted macrophages accumulate in the infected area. This factor also confers greater phagocytic power on the gathered macrophages. These so-called **angry macrophages** have more powerful destructive ability. They are especially important in defending against the bacteria that cause tuberculosis because such microbes can survive simple phagocytosis by nonactivated macrophages (see chapter opener photo).
5. One cytokine secreted by helper T cells (*IL-5*) activates eosinophils, and another (*IL-4*) promotes the development of IgE antibodies for defense against parasitic worms.

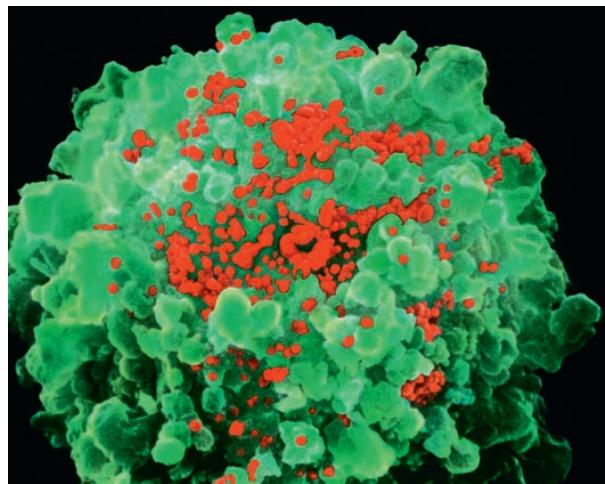
 This variety of immune activities helped by helper T cells is why **acquired immunodeficiency syndrome (AIDS)**, caused by the **human immunodeficiency virus (HIV)**, is so devastating to the immune defense system. The AIDS virus selectively invades helper (CD4+) T cells, destroying or incapacitating the cells that normally orchestrate much of the immune response (► Figure 12-16). The virus also invades macrophages, further crippling the immune system, and sometimes enters brain cells, leading to the dementia (severe impairment of intellectual capacity) noted in some AIDS victims.

HIV infections are still incurable, and efforts to develop a vaccine against HIV have been only slightly successful to date because the virus rapidly mutates. However, a variety of drugs are now available to control HIV. For example, some classes of drugs disable HIV from making copies of itself, whereas others block HIV entry into CD4+ cells. The most successful therapy is a three-drug “cocktail” that typically changes the course of the disease from a short-term death sentence to a long-term, often manageable condition. The triple combination of drugs from different classes slows progression of the condition and allows the body to replenish its CD4+ population while reducing the likelihood that the virus will develop drug resistance.

T HELPER 1 AND T HELPER 2 CELLS Not all helper cells secrete the same cytokines. Two subsets of helper T cells—**T helper 1** (T_{H1}) and **T helper 2** (T_{H2}) cells—augment different patterns of immune responses by secreting different types of cytokines. T_{H1} cells rally a cell-mediated (cytotoxic T-cell) response, which is appropriate for infections with intracellular microbes, such as viruses, whereas T_{H2} cells promote antibody-mediated immunity by B cells and rev up eosinophil activity for defense against parasitic worms.

Helper T cells produced in the thymus are in a naive state until they encounter the antigen they are primed to recognize. Whether a naive helper T cell becomes a T_{H1} or T_{H2} cell depends on which cytokines are secreted by macrophages and dendritic cells (macrophage-like cells) of the innate immune system that “present” the antigen to the uncommitted T cell. You will learn about antigen presentation in an upcoming section. **IL-12** drives a naive T cell specific for the antigen to become a T_{H1} cell, whereas **IL-4** favors the development of a naive cell into a T_{H2} cell. Thus, the antigen-presenting cells of the nonspecific immune system can influence the whole tenor of the specific immune response by determining whether the T_{H1} or T_{H2} cellular subset dominates. In the usual case, the secreted cytokines promote the appropriate specific immune response against the particular threat at hand.

Scientists have also recently discovered much smaller subsets of helper T cells: T_{H17} cells and T follicular helper (T_{FH}) cells. T_{H17} cells produce ***IL-17*** (accounting for the name of this subset). They promote inflammation and are effector molecules in the development of inflammatory autoimmune diseases such as multiple sclerosis. The newest discovered T_{FH} cells specifically interact with B cells in lymph node follicles (hence the name of this subset) to help them secrete antibodies in response to T-dependent antigens.



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► Figure 12-16 AIDS virus. Human immunodeficiency virus (HIV) (red), the AIDS-causing virus, on a helper (CD4+) T lymphocyte, HIV's primary target.

Regulatory lymphocytes suppress immune responses.

Representing 5% to 10% of CD4+ T cells, regulatory T cells suppress immune responses, thus keeping the rest of the immune system under tight control. They are specialized to inhibit both innate and adaptive immune responses in a check-and-balance fashion to minimize harmful immune pathology. T_{regs} contain large amounts of the intracellular protein Foxp3, which is essential for turning developing T cells into T_{regs} and gives these suppressor cells the ability to quiet other immune cells. Researchers hope that the ability of T_{regs} to put the brakes on helper T cells, B cells, NK cells, and dendritic (macrophage-like) cells can somehow be used therapeutically to curb autoimmune diseases and prevent rejection of transplanted organs.

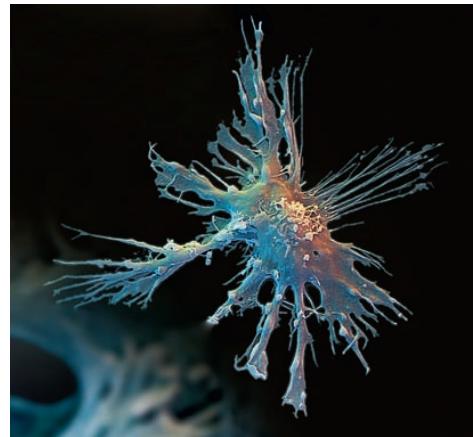
A newly discovered subset of B cells, **regulatory B cells** (B_{regs}), performs a similar role in suppressing harmful immune responses instead of turning into plasma cells that churn out antibodies as most B cells do. Constituting only about 1% to 2% of all B cells, B_{regs} help squelch autoimmunity and dampen innate-immunity directed inflammatory responses.

We next examine how T cells are activated by antigen-presenting cells and the roles of MHC molecules.

T lymphocytes respond only to antigens presented to them by antigen-presenting cells.

T cells cannot perform their tasks without assistance from antigen-presenting cells. That is, relevant T cells cannot recognize “raw” foreign antigens entering the body; before reacting to it, a T-cell clone must be formally “introduced” to the antigen. **Antigen-presenting cells (APCs)** handle the formal introduction; they engulf, then process and present antigens, complexed with MHC self-antigen molecules, on their surface to the T cells. APCs include macrophages and closely related dendritic cells, both of which not only are phagocytic effector cells of the innate defense system but also play a key role in activating cell-mediated adaptive immunity. You are already familiar with macrophages. **Dendritic cells** are specialized APCs that act as sentinels in almost every tissue. They are so named because they have many surface projections, or branches, that resemble the dendrites of neurons (*dendros* means “tree”) (► Figure 12-17). Dendritic cells are especially abundant in the skin and mucosal linings of the lungs and digestive tract—strategic locations where microbes are likely to enter the body. After exposure to the appropriate antigen, dendritic cells leave their tissue home and migrate through the lymphatic system to nearby lymph nodes, where they cluster and activate T cells.

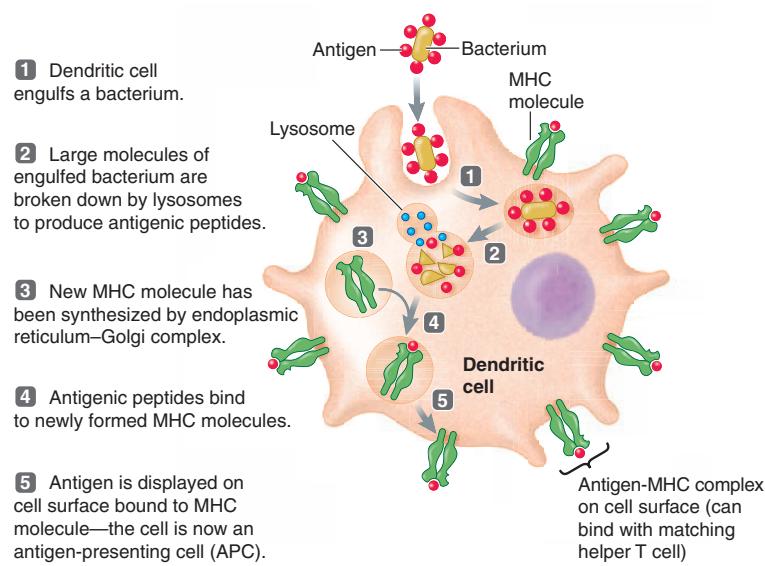
We will use a dendritic cell engulfing a bacterium and presenting it to a helper T cell as an example of an APC. Invading bacteria are phagocytized by dendritic cells (or macro-



Peter Arnold/PhotoLibrary, Inc.

► Figure 12-17 Dendritic cell.

phages) (► Figure 12-18, step 1). Within the dendritic cell, the endocytic vesicle containing the engulfed bacterium fuses with a lysosome, which enzymatically breaks down the bacterium’s proteins into antigenic peptides (small protein fragments) (step 2). Each antigenic peptide then binds to an MHC molecule, which has been newly synthesized within the endoplasmic reticulum–Golgi complex (steps 3 and 4). An MHC molecule has a deep groove into which a variety of antigenic peptides can bind, depending on what the macrophage has engulfed. The MHC molecule then transports the bound antigen to the cell surface, where it is presented to passing T lymphocytes (step 5). The dendritic cell is now an antigen-presenting cell. Once displayed at the cell surface, the combined presence of these self- and nonself antigens alerts the immune system to the presence of an undesirable agent within the cell. Unlike B cells,



► Figure 12-18 Generation of an antigen-presenting cell when a dendritic cell engulfs a bacterium.

T cells cannot bind with foreign antigen that is not in association with self-antigen. It would be futile for T cells to bind with free, extracellular antigen—they cannot defend against foreign material unless it is intracellular. Only a specific helper T cell with a T-cell receptor that fits the displayed antigen-MHC complex in complementary fashion can bind with the APC.

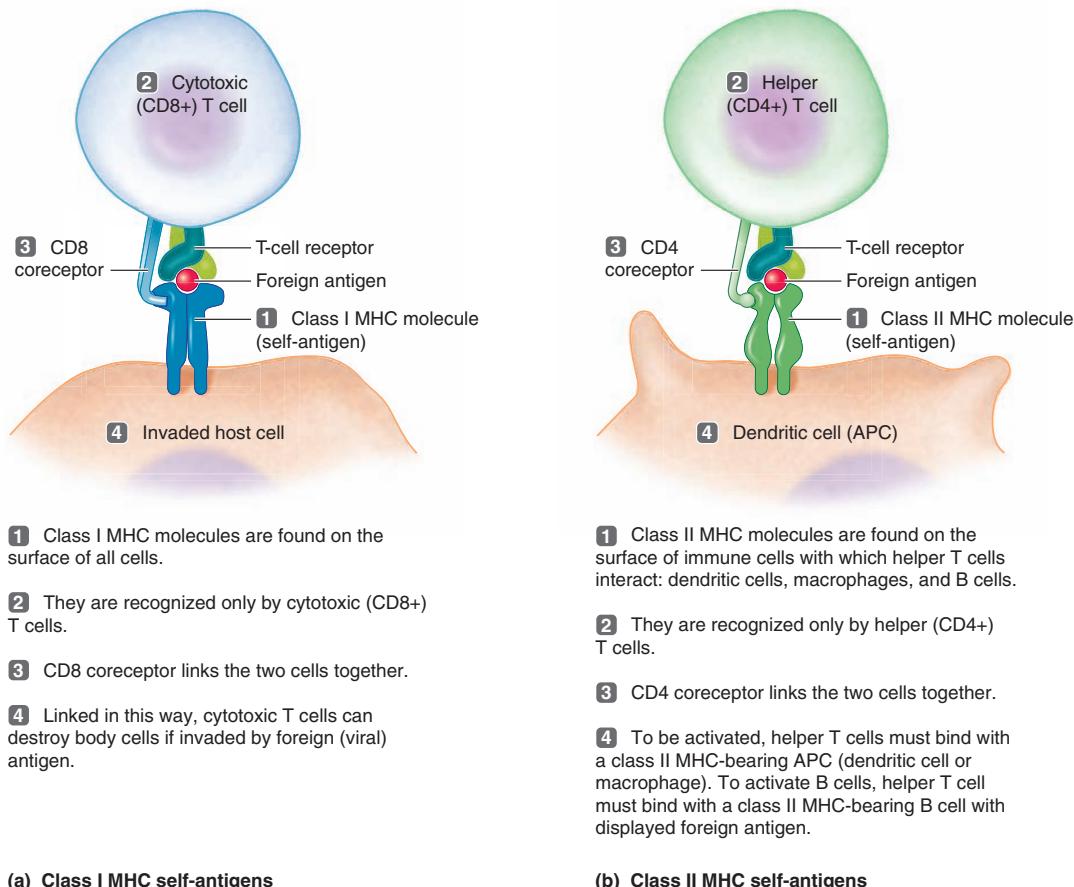
When the helper T cell binds to the APC, the APC secretes the cytokines IL-1 and TNF, which activate the associated T cell, among other effects. The activated T cell then secretes various cytokines, which act in an autocrine manner to stimulate clonal expansion of this particular helper T cell and act in a paracrine manner on adjacent B cells, cytotoxic T cells, and NK cells to enhance their responses to the same foreign antigen.

To be activated, T cells must bind with foreign antigens presented on the surface of APCs and complexed with MHC self-antigens. What is the nature of the self-antigens that the immune system learns to recognize as markers of a person's own cells? That is the topic of the next section.

The major histocompatibility complex is the code for self-antigens.

Self-antigens are plasma membrane-bound glycoproteins (proteins with sugar attached) known as **MHC molecules** because their synthesis is directed by a group of genes called the **major histocompatibility complex**, or **MHC**. This complex spans 4 million base pairs within the DNA molecule and contains 128 genes. The MHC genes are the most variable ones in humans. More than 100 different MHC molecules have been identified in human tissue, but each individual has a code for only 3 to 6 of these possible antigens. Because of the tremendous number of combinations possible, the exact pattern of MHC molecules varies from one individual to another, much like a “biochemical fingerprint” or “molecular identification card.”

The major histocompatibility complex (*histo* means “tissue”; *compatibility* means “ability to get along”) was so named because these genes and the self-antigens they encode were first



► **Figure 12-19 Distinctions between class I and class II major histocompatibility complex (MHC) glycoproteins.** Specific binding requirements for the two types of T cells ensure that these cells bind only with the target cells with which they can interact. Cytotoxic (CD8+) T cells can recognize and bind with foreign antigen only when the antigen is in association with class I MHC glycoproteins, which are found on the surface of all body cells. This requirement is met when a virus invades a body cell, whereupon the cell is destroyed by the cytotoxic T cells. Helper (CD4+) T cells, which are activated by or enhance the activities of dendritic cells, macrophages, and B cells, can recognize and bind with foreign antigen only when it is in association with class II MHC glycoproteins, which are found only on the surface of these other immune cells. The CD8+ or CD4+ T-cell's coreceptor CD8 or CD4 links these cells to the target cell's class I or class II MHC molecules, respectively.

discerned in relation to tissue typing (similar to blood typing), which is done to obtain the most compatible matches for tissue grafting and transplantation. However, the transfer of tissue from one individual to another does not normally occur in nature. The natural function of MHC antigens lies in their ability to direct the responses of T cells, not in their artificial role in rejecting transplanted tissue.

CLASS I AND CLASS II MHC GLYCOPROTEINS T cells become active only when they match a given MHC–foreign antigen combination. In addition to having to fit a specific foreign antigen, the T-cell receptor must match the appropriate MHC molecule. Each person has two main classes of MHC-encoded molecules that are differentially recognized by cytotoxic and helper T cells—**class I and class II MHC glycoproteins**, respectively (► Figure 12-19, p. 439). The class I and II markers serve as signposts to guide cytotoxic and helper T cells to the precise cellular locations where their immune capabilities can be most effective. The coreceptors (either CD8 or CD4) on the T cells bind with the MHC molecules on the target molecule, linking the two cells together.

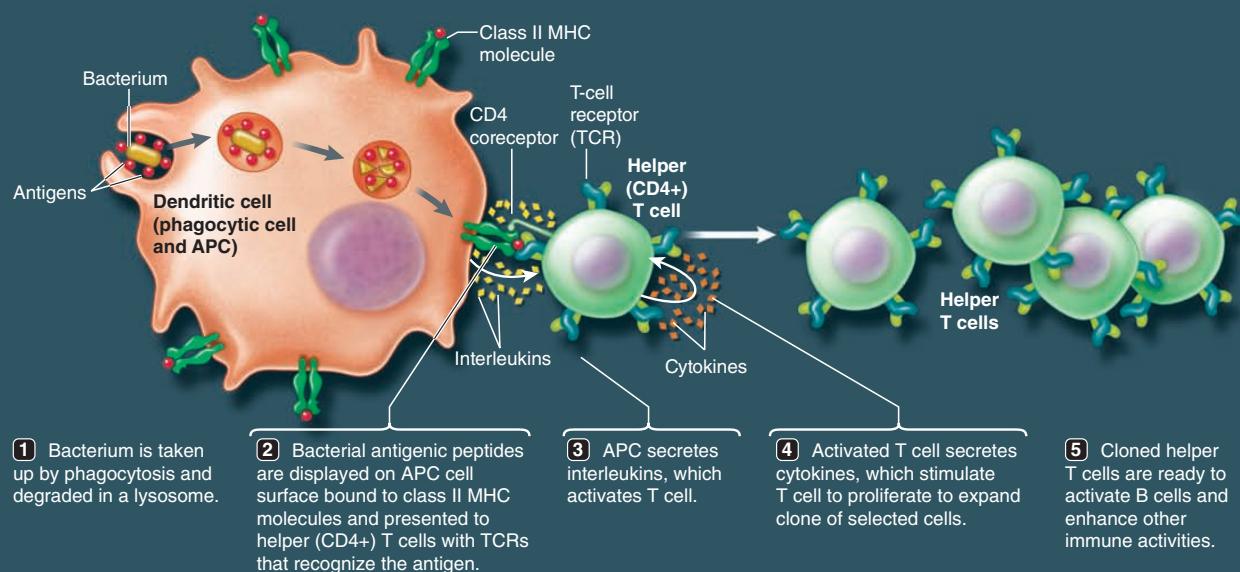
Cytotoxic (CD8+) T cells can respond to foreign antigens only in association with **class I MHC glycoproteins**, which are found on the surface of all nucleated body cells. This binding specificity occurs because the cytotoxic T cell's CD8 coreceptor can interact only with class I MHC molecules. To carry out their role of dealing with pathogens that have invaded host cells, it is appropriate that cytotoxic T cells bind only with body cells that viruses have infected—that is, with foreign antigens in association with self-antigens. Furthermore, these deadly T cells can link up with any cancerous body cell because class I MHC molecules also display mutated (and thus “foreign” appearing) cellular proteins characteristic of these abnormal cells. Because any nucleated body cell can be invaded by viruses or become cancerous, essentially all cells display class I MHC glycoproteins, enabling cytotoxic T cells to attack any virus-invaded host cell or any cancer cell. In the case

of cytotoxic T cells, the outcome of this binding is destruction of the infected body cell. Because cytotoxic T cells do not bind to MHC self-antigens in the absence of foreign antigens, normal body cells are protected from lethal immune attack.

In contrast, **class II MHC glycoproteins**, which are recognized by helper (CD4+) T cells, are restricted to the surface of a few special types of immune cells. The CD4 coreceptor associated with these helper T cells can interact only with class II MHC molecules. Thus, the specific binding requirements for cytotoxic and helper T cells ensure the appropriate T-cell responses. A helper T cell can bind with a foreign antigen only when it is found on the surfaces of immune cells with which the helper T cell directly interacts—*macrophages*, *dendritic cells*, and *B cells*. Class II MHC molecules are found on macrophages and dendritic cells, which present antigens to helper T cells and on B cells, whose activities are enhanced by cytokines secreted by helper T cells. B cells do not phagocytize antigenic particles like macrophages and dendritic cells do, but they can internalize T-dependent antigen bound to their surface receptor by receptor-mediated endocytosis (see p. 30), then display the antigens complexed with class II MHC on their surface. Binding of the antigen-bearing B cell with the matching helper T cell causes the T cell to secrete cytokines that activate this specific B cell, leading to clonal expansion and conversion of this B-cell clone into antibody-producing plasma cells and memory cells (► Figure 12-20). The capabilities of helper T cells would be squandered if these cells were able to bind with body cells other than these special APC and B immune cells. This is the primary pathway by which the adaptive immune system fights bacteria. ▀ Table 12-3 (p. 442) summarizes the innate and adaptive immune strategies that defend against bacterial invasion.

Clinical Note **TRANSPLANT REJECTION** T cells bind with MHC antigens present on the surface of transplanted cells in the absence of a foreign viral antigen. The ensuing de-

Activation of helper T cells by antigen presentation



► Figure 12-20 Interactions among large phagocytic cells (APCs), helper T cells, and B cells responsive to T-dependent antigen.

struction of the transplanted cells triggers the rejection of transplanted or grafted tissues. Presumably, some of the recipient's T cells "mistake" the MHC antigens of the donor cells for a closely resembling combination of a conventional viral foreign antigen complexed with the recipient's MHC self-antigens.

To minimize the rejection phenomenon, technicians match the tissues of donor and recipient according to MHC antigens as closely as possible. Therapeutic procedures to suppress the immune system then follow. In the past, the primary immunosuppressive tools included radiation therapy and drugs aimed at destroying the actively multiplying lymphocyte populations, plus anti-inflammatory drugs that suppressed growth of all lymphoid tissue. However, these measures not only suppressed the T cells that were primarily responsible for rejecting transplanted tissue but also depleted the antibody-secreting B cells. Unfortunately, the treated individual was left with little specific immune protection against bacterial and viral infections. In recent years, new therapeutic agents have become extremely useful in selectively depressing T-cell-mediated immune activity while leaving B-cell antibody-mediated immunity essentially intact. For example, *cyclosporin* blocks IL-2, the cytokine secreted by helper T cells that is required for expansion of the selected cytotoxic T-cell clone.

What factors normally prevent the adaptive immune system from unleashing its powerful defense capabilities against the body's own self-antigens? We examine this issue next.

The immune system is normally tolerant of self-antigens.

The term **tolerance** in this context refers to preventing the immune system from attacking the person's own tissues. During the genetic "cut, shuffle, and paste process" that goes on during lymphocyte development, some B and T cells are by chance formed that could react against the body's own tissue antigens.

If these lymphocyte clones were allowed to function, they would destroy the individual's own body. Fortunately, the immune system normally does not produce antibodies or activated T cells against the body's own self-antigens.

At least eight different mechanisms are involved in tolerance:

- 1. Clonal deletion.** In response to continuous exposure to body antigens early in development, B and T lymphocyte clones specifically capable of attacking these self-antigens in most cases are permanently destroyed within the thymus. This **clonal deletion** is accomplished by triggering apoptosis of immature cells that would react with the body's own proteins. This physical elimination is the major mechanism by which tolerance is developed.
- 2. Clonal anergy.** The premise of clonal anergy is that a T lymphocyte must receive two specific simultaneous signals to be activated ("turned on"), one from its compatible antigen and a stimulatory cosignal molecule known as **B7** found only on the surface of an APC. Both signals are present for foreign antigens, which are introduced to T cells by APCs. Once a T cell is turned on by finding its matching antigen in accompaniment with the cosignal, the cell no longer needs the co-signal to interact with other cells. For example, an activated cytotoxic T cell can destroy any virus-invaded cell that bears the viral antigen even though the infected cell does not have the cosignal. In contrast, these dual signals—antigen plus co-signal—never are present for self-antigens because these antigens are not handled by cosignal-bearing APCs. The first exposure to a single signal from a self-antigen "turns off" the compatible T cell, rendering the cell unresponsive to further exposure to the antigen. This reaction is referred to as **clonal anergy** (*anergy* means "lack of energy") because T cells are inactivated (that is, "become lazy") rather than activated by their antigens. Anergized T lymphocyte clones survive, but they can't function.

Activation of B cells responsive to T-dependent antigen

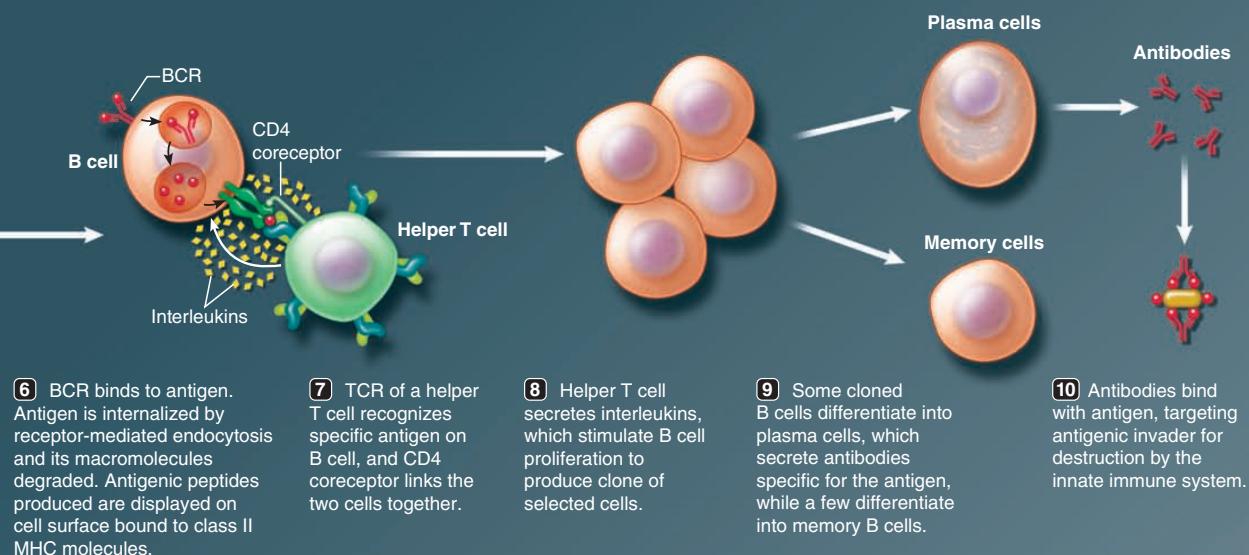


TABLE 12-3 Innate and Adaptive Immune Responses to Bacterial Invasion

INNATE IMMUNE MECHANISMS	ADAPTIVE IMMUNE MECHANISMS
Roles of Inflammation Resident tissue macrophages engulf invading bacteria. Histamine-induced vascular responses increase blood flow to the area, bringing in additional immune-effector cells and plasma proteins. A fibrin clot walls off the invaded area. Neutrophils and monocytes—macrophages migrate from the blood to the area to engulf and destroy foreign invaders and to remove cell debris. Phagocytic cells secrete cytokines, which enhance both innate and adaptive immune responses and induce local and systemic symptoms associated with an infection.	Roles of B Cells and Helper T Cells B cells specific to T-independent antigen are activated on binding with the antigen. B cells specific to T-dependent antigen present antigen to helper T cells. On binding with the B cells, helper T cells activate the B cells. The activated B-cell clone proliferates and differentiates into plasma cells and memory cells. Plasma cells secrete customized antibodies, which specifically bind to the invading bacteria. Plasma cell activity is enhanced by IL-1 secreted by macrophages Helper T cells, which have been activated by the same bacterial antigen processed and presented to them by macrophages or dendritic cells
Roles of the Complement System The complement system is nonspecifically activated by exposure to PAMPs (alternate complement pathway). Complement components form a hole-punching membrane attack complex that lyses bacterial cells. Complement components enhance many steps of inflammation.	Antibodies bind to invading bacteria and enhance innate mechanisms that lead to the bacteria's destruction. Specifically, antibodies Act as opsonins to enhance phagocytic activity Activate the lethal complement system (classical complement pathway) Stimulate natural killer (NK) cells, which directly lyse bacteria
	Memory cells persist that are capable of responding more rapidly and more forcefully should the same bacteria be encountered again.

3. *Receptor editing.* With **receptor editing**, once a B cell that bears a receptor for one of the body's own antigens encounters the self-antigen, the B cell escapes death by swiftly changing its antigen receptor to a nonself version. In this way, an originally self-reactive B cell survives but is "rehabilitated" so that it will never target the body's own tissues again.

4. *Active suppression by regulatory cells.* T_{reg} s (and possibly B_{reg} s) play a role in tolerance by inhibiting throughout life some lymphocyte clones specific for the body's own tissues.

5. *Immunological ignorance,* alternatively known as *antigen sequestering.* Some self-molecules are normally hidden from the immune system because they never come into direct contact with the ECF in which the immune cells and their products circulate. An example of such a segregated antigen is *thyroglobulin*, a complex protein sequestered within the hormone-secreting structures of the thyroid gland (see p. 686).

6. *Immune privilege.* A few tissues, most notably the testes and the eyes, have **immune privilege** because they escape immune attack even when they are transplanted in an unrelated individual. Scientists recently discovered that the cellular plasma membranes in these immune-privileged tissues have a specific

molecule that triggers apoptosis of approaching activated lymphocytes that could attack the tissues.

7. *Activation-induced cell death* comes about in some instances as a result of overactivation of self-reactive B cells.

8. *Release of anti-inflammatory IL-10.* A variety of immune cells— $T_{H}2$, cytotoxic T cells, T_{reg} s, B cells, B_{reg} s, mast cells, and eosinophils—release **IL-10**, a cytokine with broad anti-inflammatory properties that inhibits both macrophages and dendritic cells, including depressing their production of inflammation-producing cytokines. Through this inhibitory action, IL-10 helps in check-and-balance fashion put the brake on immune attacks against both self- and environmental antigens.

Autoimmune diseases arise from loss of tolerance to self-antigens.

 Occasionally, the immune system fails to distinguish between self-antigens and foreign antigens and unleashes its deadly powers against one or more of the body's own tissues. A condition in which the immune system fails to recognize and tolerate self-antigens associated with par-

ticular tissues is known as an **autoimmune disease** (*auto* means “self”). Autoimmune diseases arise from a combination of genetic predisposition and environmental insults that lead to failure of the immune system’s tolerance mechanisms. Autoimmunity underlies more than 80 diseases, many of which are well known. Examples include *multiple sclerosis*, *rheumatoid arthritis*, *Type 1 diabetes mellitus*, and *psoriasis*. About 50 million Americans suffer from some type of autoimmune disease, with the incidence being about three times higher in females than in males. Autoimmune diseases affect 1 in 20 people worldwide.

Autoimmune diseases may arise from a number of different causes:

1. Exposure of normally inaccessible self-antigens sometimes induces an immune attack against these antigens. Because the immune system is usually never exposed to hidden self-antigens, it does not “learn” to tolerate them. Inadvertent exposure of these normally inaccessible antigens to the immune system because of tissue disruption caused by injury or disease can lead to a rapid immune attack against the affected tissue, just as if these self-proteins were foreign invaders. *Hashimoto’s disease*, which involves production of antibodies against thyroglobulin and destruction of the thyroid gland’s hormone-secreting capacity, is one such example.
2. Normal self-antigens may be modified by factors such as drugs, environmental chemicals, viruses, or genetic mutations so that they are no longer recognized and tolerated by the immune system.
3. Exposure of the immune system to a foreign antigen structurally almost identical to a self-antigen may induce the production of antibodies or activated T lymphocytes that not only interact with the foreign antigen but also cross-react with the closely similar body antigen. An example of this molecular mimicry is the streptococcal bacteria responsible for “strep throat.” The bacteria possess antigens structurally very similar to self-antigens in the tissue covering the heart valves of some individuals, in which case the antibodies produced against the streptococcal organisms may also bind with this heart tissue. The resultant inflammatory response is responsible for the heart-valve lesions associated with *rheumatic fever*.
4. New studies hint at another possible trigger of autoimmune diseases, one that could explain why a whole host of these disorders are more common in women than in men. Traditionally, scientists have speculated that the sex bias of autoimmune diseases was somehow related to hormonal differences. Recent findings suggest, however, that the higher incidence of these self-destructive conditions in females may be a legacy of pregnancy. Researchers have learned that fetal cells, which often gain access to the mother’s bloodstream during the trauma of labor and delivery, sometimes linger in the mother for decades after the pregnancy. The immune system typically clears these cells from the mother’s body following childbirth, but studies involving autoimmune diseases demonstrated that women with these conditions were more likely than healthy women to have persistent fetal cells in their blood. The persistence of similar but not identical fetal antigens that were not wiped out early on as being foreigners may somehow trigger a gradual, more subtle immune

attack that eventually turns against the mother’s own closely related antigens. For example, this phenomenon might be the underlying trigger for *systemic lupus erythematosus*, an autoimmune attack against DNA, a condition that can affect many organs, most commonly skin, joints, and kidneys.

Let us now look in more detail at the role of T cells in defending against cancer.

Immune surveillance against cancer cells involves an interplay among immune cells and interferon.

Besides destroying virus-infected host cells, an important function of the T-cell system is recognizing and destroying newly arisen, potentially cancerous tumor cells before they have a chance to multiply and spread, a process known as **immune surveillance**. At least once a day, on average, your immune system destroys a mutated cell that could potentially become cancerous. Any normal cell may be transformed into a cancer cell if mutations occur within its genes that govern cell division and growth. Such mutations may occur by chance alone or, more frequently, by exposure to **carcinogenic** (cancer-causing) **factors** such as ionizing radiation, certain environmental chemicals, or physical irritants. Alternatively, a few cancers are caused by tumor viruses, which turn the cells they invade into cancer cells, an example being the *human papillomavirus* that causes cervical cancer. The immune system recognizes cancer cells because they bear new and different surface antigens alongside the cell’s normal self-antigens because of either genetic mutation or invasion by a tumor virus.



BENIGN AND MALIGNANT TUMORS Cell multiplication and growth are normally under strict control, but the regulatory mechanisms are largely unknown. Cell multiplication in an adult is generally restricted to replacing lost cells. Furthermore, cells normally respect their own place and space in the body’s society of cells. If a cell that has transformed into a tumor cell manages to escape immune destruction, however, it defies the normal controls on its proliferation and position. Unrestricted multiplication of a single tumor cell results in a **tumor** that consists of a clone of cells identical to the original mutated cell.

If the mass is slow growing, stays put in its original location, and does not infiltrate the surrounding tissue, it is considered a **benign tumor**. In contrast, the transformed cell may multiply rapidly and form an invasive mass that lacks the “altruistic” behavior characteristic of normal cells. Such invasive tumors are **malignant tumors**, or **cancer**. Malignant tumor cells usually do not adhere well to the neighboring normal cells, so often some of the cancer cells break away from the parent tumor. These “emigrant” cancer cells are transported through the blood to new territories, where they continue to proliferate, forming multiple malignant tumors. The term **metastasis** is applied to this spreading of cancer to other parts of the body.

If a malignant tumor is detected early, before it has metastasized, it can be removed surgically. Once cancer cells have dispersed and seeded multiple cancerous sites, surgical elimination of the malignancy is impossible. In this case, agents that

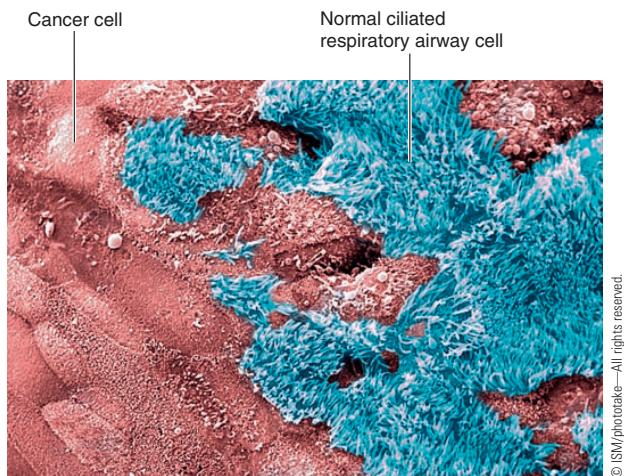


Figure 12-21 Comparison of normal and cancerous cells in the large respiratory airways. The normal cells display specialized cilia (blue), which constantly contract in whiplike motion to sweep debris and microorganisms from the respiratory airways so that they do not gain entrance to the deeper portions of the lungs. The cancerous cells are not ciliated, so they are unable to perform this specialized defense task.

interfere with rapidly dividing and growing cells, such as certain chemotherapy drugs, are used in an attempt to destroy the malignant cells. Unfortunately, these agents also harm normal body cells, especially rapidly proliferating cells such as blood cells and the cells lining the digestive tract.

Untreated cancer is eventually fatal in most cases, for several interrelated reasons. The uncontrollably growing malignant mass crowds out normal cells by vigorously competing with them for space and nutrients, yet the cancer cells cannot take over the functions of the cells they are destroying. Cancer cells typically remain immature and do not become specialized, often resembling embryonic cells instead (Figure 12-21). Such poorly differentiated malignant cells lack the ability to perform the specialized functions of the normal cell type from which they mutated. Affected organs gradually become disrupted to the point that they can no longer perform their life-sustaining functions, and the person dies.

GENETIC MUTATIONS THAT DO NOT LEAD TO CANCER

TO CANCER Even though many body cells undergo mutations throughout a person's lifetime, most of these mutations do not result in malignancy for three reasons:

1. Only a fraction of the mutations involve loss of control over the cell's growth and multiplication. More frequently, other facets of cellular function are altered.
2. A cell usually becomes cancerous only after an accumulation of multiple independent mutations. This requirement contributes at least in part to the

much higher incidence of cancer in older individuals, in whom mutations have had more time to accumulate in a single cell lineage.

3. Potentially cancerous cells that do arise are usually destroyed by the immune system early in their development.

EFFECTORS OF IMMUNE SURVEILLANCE Immune surveillance against cancer depends on an interplay among three types of immune cells—*cytotoxic T cells*, *NK cells*, and *macrophages*—and *interferon*. These three immune cell types not only can attack and destroy cancer cells directly but also secrete interferon. Interferon, in turn, inhibits multiplication of cancer cells and increases the killing ability of the immune cells (Figure 12-22).

Because NK cells do not require prior exposure and activation in response to a cancer cell before being able to launch a lethal attack, they are the first line of defense against cancer. In addition, cytotoxic T cells take aim at cancer cells after being activated by mutated surface proteins alongside normal class I MHC molecules. On contacting a cancer cell, both these killer cells release perforin and other toxic chemicals that destroy the targeted mutant cell (Figure 12-22). Macrophages, in addition to clearing away the remains of the dead victim cell, can engulf and destroy cancer cells intracellularly.

Still, cancer does sometimes occur because cancer cells occasionally escape these immune mechanisms. Some cancer cells are believed to survive by evading immune detection—for example, by failing to display identifying antigens on their surface or by being surrounded by counterproductive **blocking antibodies** that interfere with T-cell function. Although B cells and antibodies are not believed to play a direct role in cancer defense, B cells, on

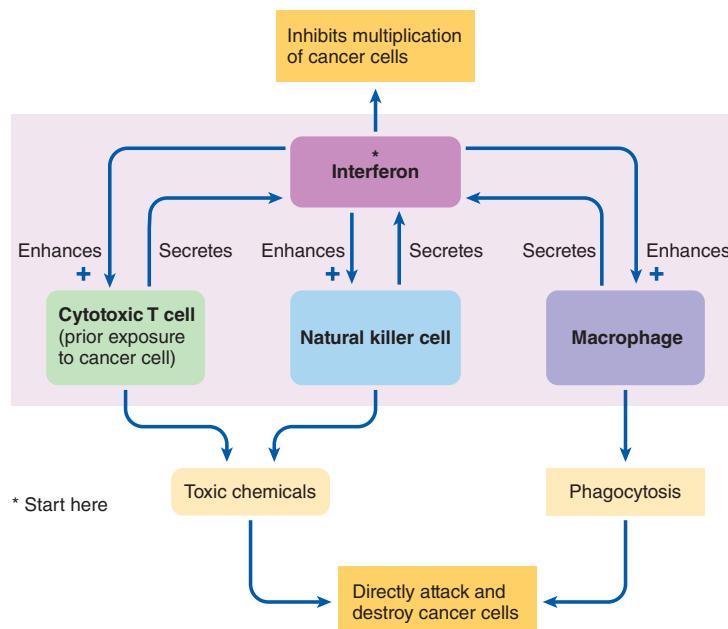


Figure 12-22 Immune surveillance against cancer. Anticancer interactions of cytotoxic T cells, natural killer cells, macrophages, and interferon.

viewing a mutant cancer cell as an alien to “normal self,” may produce antibodies against it. These antibodies, for unknown reasons, do not activate the complement system, which could destroy the cancer cells. Instead, the antibodies bind with the antigenic sites on the cancer cell, “hiding” these sites from recognition by cytotoxic T cells. The coating of a tumor cell, by blocking antibodies, thus protects the harmful cell from attack by deadly T cells. Still other successful cancer cells thwart immune attack by turning on their pursuers. They induce the cytotoxic T cells that bind with them to commit suicide. In addition, some cancer cells secrete large amounts of a specific chemical messenger that recruits T_{reg} s and programs them to suppress cytotoxic T cells.

We have completed our discussion of the B and T cells. Table 12-4 compares the properties of these two adaptive effector cells.

A regulatory loop links the immune system with the nervous and endocrine systems.

Even though complex controlling factors operate within the immune system itself, until recently scientists thought that the immune system functioned independently of other control systems in the body. However, they now know that the immune system both influences and is influenced by the two major regulatory systems, the nervous and endocrine systems. For example, IL-1 can turn on the stress response by activating a sequence of nervous and endocrine events that result in the secretion of cortisol, one of the major hormones released during stress. This linkage between a mediator of the immune response and a mediator of the stress response is appropriate. Cortisol mobilizes the body’s nutrient stores so that metabolic fuel is readily available to keep pace with the body’s energy de-

mands at a time when the person is sick and may not be eating enough (or, in the case of an animal, may not be able to search for food). Furthermore, cortisol mobilizes amino acids, which serve as building blocks to repair any tissue damage sustained during the encounter that triggered the immune response.

In the reverse direction, lymphocytes and macrophages are responsive to blood-borne signals from the nervous system and from certain endocrine glands. These important immune cells possess receptors for a wide variety of neurotransmitters, hormones, and other chemical mediators. For example, cortisol and other chemical mediators of the stress response have a profound immunosuppressive effect, inhibiting many functions of lymphocytes and macrophages and decreasing the production of cytokines. Thus, a negative-feedback loop exists among the immune system and the nervous and endocrine systems. Cytokines released by immune cells enhance the neurally and hormonally controlled stress response, whereas cortisol and related chemical mediators released during the stress response suppress the immune system. For example, the anti-inflammatory effect of cortisol modulates stress-activated immune responses, preventing them from overshooting, and thus protecting us against damage by potentially overreactive defense mechanisms.

However, in large part because stress suppresses the immune system, stressful physical, psychological, and social life events are sometimes linked with increased susceptibility to infections and cancer. Thus, the body’s resistance to disease can be influenced by the person’s mental state—a case of “mind over matter.”

Other important links exist between the immune and nervous systems besides the cortisol connection. For example, many immune system organs, such as the thymus, spleen, and lymph nodes, are innervated by the sympathetic nervous system, the branch of the nervous system called into play during stress-related

TABLE 12-4 B versus T Lymphocytes

Characteristic	B Lymphocytes	T Lymphocytes
Ancestral origin	Bone marrow	Bone marrow
Site of maturational processing	Bone marrow	Thymus
Receptors for antigen	B-cell receptors are antibodies inserted in the plasma membrane; highly specific	T-cell receptors present in the plasma membrane are not the same as antibodies; highly specific
Bind with	Extracellular antigens such as bacteria, free viruses, and other circulating foreign material	Foreign antigen in association with self-antigen, such as virus-infected cells
Types of active cells	Plasma cells	Cytotoxic T cells, helper T cells, regulatory T cells
Formation of memory cells	Yes	Yes
Type of immunity	Antibody-mediated immunity	Cell-mediated immunity
Secretory product	Antibodies	Cytokines
Functions	Help eliminate free foreign invaders (mostly bacteria) by enhancing innate immune responses against them	Lysse virus-infected cells and cancer cells; aid B cells in antibody production; modulate immune responses
Life span	Short	Long

Exercise: A Help or Hindrance to Immune Defense?

FOR YEARS PEOPLE WHO ENGAGE IN MODERATE EXERCISE REGULARLY have claimed they have fewer colds when they are in good aerobic condition. In contrast, elite athletes and their coaches have often complained about the number of upper respiratory infections that the athletes seem to contract at the height of their competitive seasons. The results of recent scientific studies lend support to both these claims. The impact of exercise on immune defense depends on the intensity of the exercise.

Animal studies have shown that high-intensity exercise after experimentally induced infection results in more severe infection. Moderate exercise performed prior to infection or to tumor implantation, in contrast, results in less severe infection and slower tumor growth in experimental animals.

Studies on humans lend further support to the hypothesis that exhaustive exercise suppresses immune defense, whereas moderate exercise stimulates the immune system. A survey of 2300 runners competing in a major marathon indicated that those who ran more than 60 miles a week had twice the number of respiratory infections as those who ran less than 20 miles a week in the two months preceding the race. In another study, 10 elite athletes were asked to run

on a treadmill for 3 hours at the same pace they would run in competition. Blood tests after the run indicated that natural killer (NK) cell activity had decreased by 25% to 50%, and this decrease lasted for 6 hours. The runners also showed a 60% increase in the stress hormone cortisol, which is known to suppress immunity. Other studies have shown that athletes have lower resting salivary IgA levels compared with control subjects and that their respiratory mucosal immunoglobulins are decreased after prolonged exhaustive exercise. These results suggest a lower resistance to respiratory infection following high-intensity exercise. Because of these results, researchers in the field recommend that athletes keep exposure to respiratory viruses to a minimum by avoiding crowded places or anyone with a cold or flu for the first 6 hours after strenuous competition.

However, a study evaluating the effects of a moderate exercise program in which a group of women walked 45 minutes a day, 5 days a week, for 15 weeks found that the walkers' antibody levels and NK cell activity increased throughout the exercise program. Other studies using moderate exercise on stationary bicycles in subjects older than age 65 showed increases in NK cell activity as large as those found in young people.

"fight-or-flight" situations (see p. 244). Also, a parasympathetic anti-inflammatory pathway helps rein in the inflammatory response. The vagus nerve, the main nerve of the parasympathetic nervous system, supplies the spleen and other sites where macrophages are abundant. Macrophages, the orchestrators of many aspects of inflammation, have receptors for acetylcholine (ACh), the parasympathetic postganglionic neurotransmitter. Through this means, ACh suppresses inflammation. In the reverse direction, immune system secretions act on the brain to produce fever and other general symptoms that accompany infections. Furthermore, immune cells secrete some traditional hormones once thought to be produced only by the endocrine system. For example, many of the hormones secreted by the pituitary gland are produced by lymphocytes as well. Scientists are only beginning to sort out the mechanisms and implications of the many complex neuro-endocrine-immune interactions. (For a discussion of the possible effects of exercise on immune defense, see the accompanying boxed feature, ■ A Closer Look at Exercise Physiology.)

Check Your Understanding 12.5

1. List the three major types of T cells and state their functions.
2. Describe the role of antigen-presenting cells.
3. Define *immune surveillance* and discuss how it is accomplished.

12.6 Immune Diseases

Abnormal functioning of the immune system can lead to immune diseases in two general ways: *immunodeficiency diseases* (too little immune response) and *inappropriate immune attacks* (too much or mistargeted immune response).

Immunodeficiency diseases result from insufficient immune responses.

 **Immunodeficiency diseases** occur when the immune system fails to respond adequately to foreign invasion.

The condition may be congenital (present at birth) or acquired (nonhereditary), and it may involve impairment of antibody-mediated or cell-mediated immunity, or both.

In a rare hereditary condition known as **severe combined immunodeficiency**, both B and T cells are lacking. Such people have extremely limited defenses against pathogenic organisms and die in infancy unless maintained in a germ-free environment (that is, live in a "bubble"). However, that verdict has changed with recent successes using gene therapy to cure the disease in some patients.

Acquired (nonhereditary) immunodeficiency states can arise from inadvertent destruction of lymphoid tissue during prolonged therapy with anti-inflammatory agents, such as cortisol derivatives, or from cancer therapy aimed at destroying rapidly dividing cells (which unfortunately include lympho-

cytes as well as cancer cells). The most recent and tragically the most common acquired immunodeficiency disease is AIDS, which, as described earlier, is caused by HIV, a virus that invades and incapacitates the critical helper T cells.

Let us now look at inappropriate immune attacks.

Allergies are inappropriate immune attacks against harmless environmental substances.



Inappropriate immune attacks cause reactions harmful to the body. These include (1) *autoimmune diseases*, in which the immune system turns against one of the body's own tissues (see p. 442); (2) *immune complex diseases*, which involve overexuberant antibody responses that "spill over" and damage normal tissue (see p. 430); and (3) allergies. The first two conditions have been described earlier in this chapter, so we now concentrate on allergies.

An **allergy** is the acquisition of an inappropriate specific immune reactivity, or **hypersensitivity**, to a normally harmless environmental substance, such as dust or pollen. The offending agent is known as an **allergen**. Subsequent reexposure of a sensitized individual to the same allergen elicits an immune attack, which may vary from a mild, annoying reaction to a severe, body-damaging reaction that may even be fatal.

Allergic responses are classified into two categories: immediate hypersensitivity and delayed hypersensitivity. In **immediate hypersensitivity**, the allergic response appears within about 20 minutes after a sensitized person is exposed to an allergen. In **delayed hypersensitivity**, the reaction does not generally show up until a day or so following exposure. The difference in timing is the result of the different mediators involved. A particular allergen may activate either a B- or a T-cell response. Immediate allergic reactions involve B cells and are elicited by antibody interactions with an allergen; delayed reactions involve T cells and the more slowly responding process of cell-mediated immunity against the allergen. Let us examine the causes and consequences of each of these reactions in more detail.

TRIGGERS FOR IMMEDIATE HYPERSENSITIVITY In immediate hypersensitivity, the antibodies involved and the events that ensue on exposure to an allergen differ from the typical antibody-mediated response to bacteria. The most common allergens that provoke immediate hypersensitivities are pollen grains, bee stings, penicillin, certain foods, molds, dust, feathers, and animal fur. (Actually, people allergic to cats are not allergic to the fur itself. The true allergen is in the cat's saliva, which is deposited on the fur during licking. Likewise, people are not allergic to dust or feathers per se but to tiny mites that inhabit the dust or feathers and eat the scales constantly being shed from the skin.) For unclear reasons, these allergens bind to and elicit the synthesis of IgE antibodies rather than the IgG antibodies associated with bacterial antigens. IgE antibodies are the least plentiful immunoglobulin, but their presence spells trouble. Without IgE antibodies, there would be no immediate hypersensitivity. When a person with an allergic tendency is first exposed to a particular allergen, compatible helper T cells secrete IL-4, a cytokine that prods compatible B cells to synthesize IgE antibodies specific for the allergen. During this initial

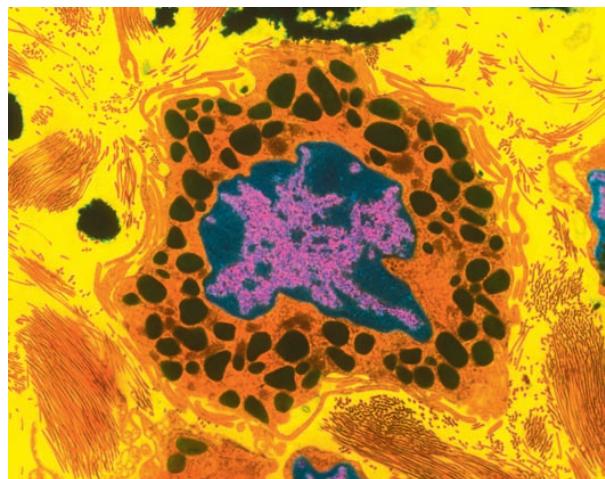
sensitization period no symptoms are evoked, but memory cells form that are primed for a more powerful response on subsequent reexposure to the same allergen.

In contrast to the antibody-mediated response elicited by bacterial antigens, IgE antibodies do not freely circulate. Instead, their tail portions attach to mast cells and basophils, both of which produce and store an arsenal of potent inflammatory chemicals, such as histamine, in preformed granules (► Figure 12-23). Mast cells are most plentiful in regions that come into contact with the external environment, such as the skin, the outer surface of the eyes, and the linings of the respiratory system and digestive tract. Binding of an appropriate allergen with the outreached arm regions of the IgE antibodies that are lodged tail-first in a mast cell or basophil triggers the rupture of the cell's granules. As a result, histamine and other chemical mediators spew forth into the surrounding tissue.

A single mast cell (or basophil) may be coated with several different IgE antibodies, each able to bind with a different allergen. Thus, the mast cell can be triggered to release its chemical products by any one of several allergens (► Figure 12-24).

CHEMICAL MEDIATORS OF IMMEDIATE HYPERSENSITIVITY These released chemicals cause the reactions that characterize immediate hypersensitivity. The following are among the most important chemicals released during immediate allergic reactions:

1. **Histamine**, which brings about vasodilation and increased capillary permeability and increased mucus production.
2. **Slow-reactive substance of anaphylaxis (SRS-A)**, which induces prolonged and profound contraction of smooth muscle, especially of the small respiratory airways. SRS-A is a col-

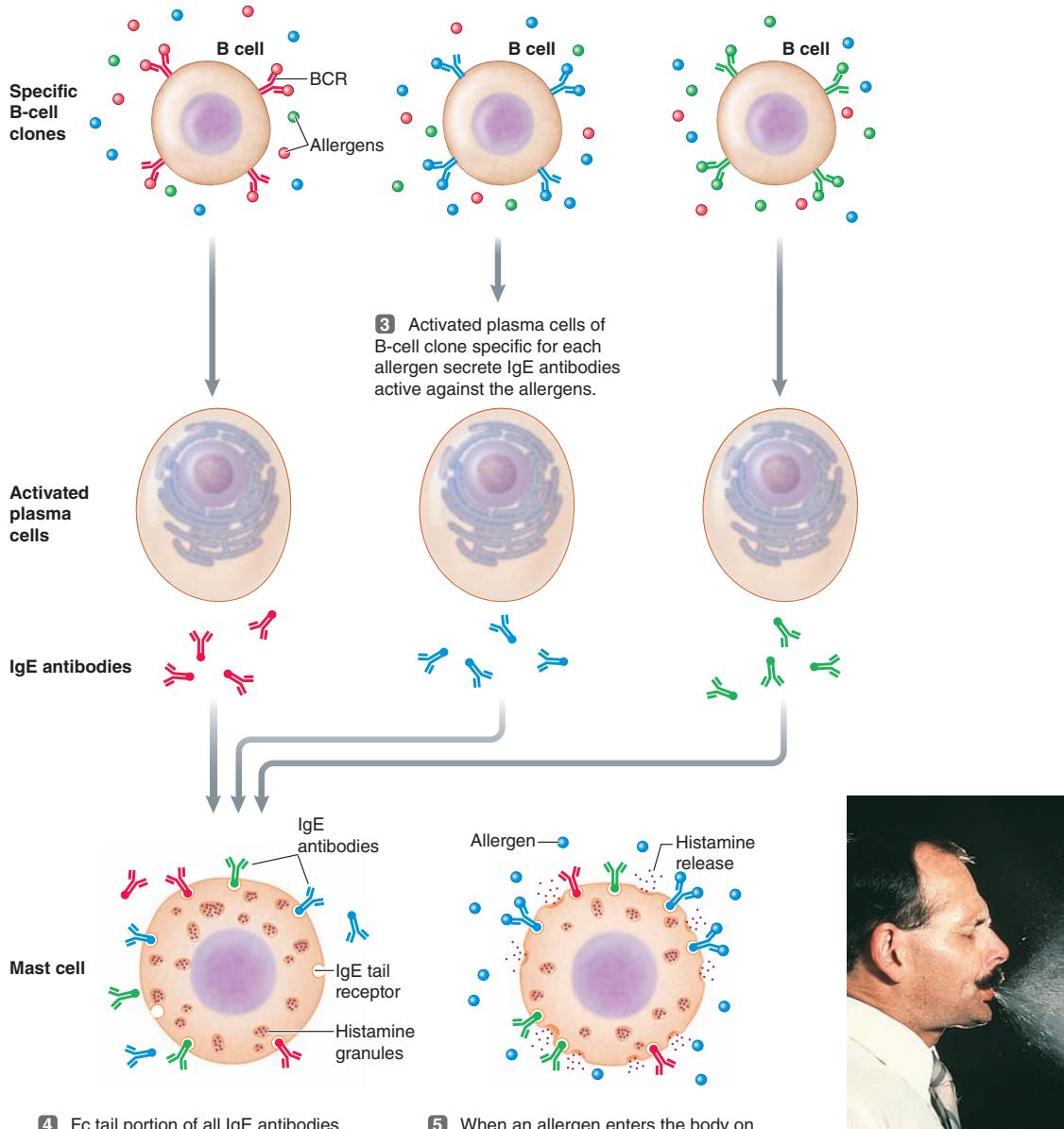


Steve Gschmeissner/Photo Researchers, Inc.

► Figure 12-23 **Mast cell.** Transmission electron micrograph through a section of a mast cell within connective tissue. Note the numerous granules (black) in the cytoplasm (brown) surrounding the nucleus (purple and dark blue). The preformed granules contain histamine and other chemical mediators of immediate hypersensitivity that are released on binding of an allergen.

1 Allergens (antigens) enter the body for the first time.

2 Allergens bind to matching BCRs; B cells now process the allergens and, with stimulation by helper T cells (not shown), proceed through the steps leading to clonal expansion of activated plasma cells.



4 Fc tail portion of all IgE antibodies, regardless of the specificity of their Fab arm regions, binds to IgE tail receptors on mast cells and basophils. Unlike B cells, each mast cell can have a variety of antibody surface receptors for binding different allergens.

5 When an allergen enters the body on subsequent exposure, it binds with its matching IgE antibodies on mast cells; binding stimulates the mast cell to release histamine and other substances by exocytosis. Any allergen for which preformed, matching IgE are attached to the mast cell can trigger histamine release.

6 Histamine and other released chemicals elicit the allergic response.

Figure 12-24 Role of IgE antibodies and mast cells in immediate hypersensitivity. B-cell clones are converted into plasma cells, which secrete IgE antibodies on contact with the allergen for which they are specific. All IgE antibodies, regardless of their antigen specificity, bind to mast cells or basophils. When an allergen combines with the IgE receptor specific for it on the surface of a mast cell, the mast cell releases histamine and other chemicals from preformed granules by exocytosis. These chemicals elicit the allergic response.

lection of three related *leukotrienes*, locally acting mediators similar to prostaglandins (see p. 753).

3. **Eosinophil chemotactic factor**, which specifically attracts eosinophils to the area. Interestingly, eosinophils release enzymes that inactivate SRS-A and may inhibit histamine, perhaps serving as an “off switch” to limit the allergic response.

SYMPTOMS OF IMMEDIATE HYPERSENSITIVITY Symptoms of immediate hypersensitivity vary depending on the site, allergen, and mediators involved. Most frequently, the reaction is localized to the body site in which the IgE-bearing cells first come into contact with the allergen. If the reaction is limited to the upper respiratory passages after a person inhales an allergen such as ragweed pollen, the released chemicals bring about the symptoms characteristic of **hay fever**—for example, nasal congestion caused by histamine-induced localized edema and sneezing and runny nose caused by increased mucus secretion. If the reaction is concentrated primarily within the bronchioles (the small respiratory airways that lead to the tiny air sacs within the lungs), **asthma** results. Contraction of the smooth muscle in the walls of the bronchioles in response to SRS-A narrows or constricts these passageways, making breathing difficult. Localized swelling in the skin because of allergy-induced histamine release causes **hives**. An allergic reaction in the digestive tract in response to an ingested allergen can lead to diarrhea.

TREATMENT OF IMMEDIATE HYPERSENSITIVITY Treatment of localized immediate allergic reactions with antihistamines often offers only partial relief of the symptoms because some manifestations are invoked by other chemical mediators not blocked by these drugs. For example, antihistamines are not particularly effective in treating asthma, the most serious symptoms of which are invoked by SRS-A. Adrenergic drugs (which mimic the sympathetic nervous system; see p. 247) are helpful through their vasoconstrictor-bronchodilator actions in counteracting the effects of both histamine and SRS-A. Anti-inflammatory drugs such as cortisol derivatives are often used as the primary treatment for ongoing allergen-induced inflammation, such as that associated with asthma. Newer drugs such as *Singulair* that inhibit leukotrienes, including SRS-A, have been added to the arsenal for combating immediate allergies.

ANAPHYLACTIC SHOCK A life-threatening systemic reaction can occur if the allergen becomes blood borne or if very large amounts of chemicals are released from the localized site into the circulation. When large amounts of these chemical mediators gain access to the blood, the extremely serious systemic (involving the entire body) reaction known as **anaphylactic shock** occurs. Severe hypotension that can lead to circulatory shock (see p. 383) results from widespread vasodilation and a massive shift of plasma fluid into the interstitial spaces as a result of a generalized increase in capillary permeability. Concurrently, pronounced bronchiolar constriction occurs and can lead to respiratory failure. The person may suffo-

cate from an inability to move air through the narrowed airways. Unless countermeasures, such as injecting a vasoconstrictor-bronchodilator drug, are undertaken immediately, anaphylactic shock is often fatal. This reaction is the reason even a single bee sting or eating a peanut can be so dangerous in people sensitized to these allergens.

IMMEDIATE HYPERSENSITIVITY AND ABSENCE OF PARASITIC WORMS Although the immediate hypersensitivity response differs considerably from the typical IgG antibody response to bacterial infections, it is strikingly similar to the immune response elicited by parasitic worms. Shared characteristics of the immune reactions to allergens and parasitic worms include the production of IgE antibodies and increased basophil and eosinophil activity. This finding has led to the proposal that harmless allergens somehow trigger an immune response designed to fight worms. Mast cells are concentrated in areas where parasitic worms (and allergens) could contact the body. Parasitic worms can penetrate the skin or digestive tract or can attach to the digestive tract lining. Some worms migrate through the lungs during a part of their life cycle. Scientists suspect the IgE response helps ward off these invaders as follows. The inflammatory response in the skin could wall off parasitic worms attempting to burrow in. Coughing and sneezing could expel worms that migrated to the lungs. Diarrhea could help flush out worms before they could penetrate or attach to the digestive tract lining. Interestingly, epidemiological studies suggest that the incidence of allergies in a country rises as the presence of parasites decreases. Thus, superfluous immediate hypersensitivity responses to normally harmless allergens may represent a pointless marshaling of a honed immune-response system “with nothing better to do” in the absence of parasitic worms.

DELAYED HYPERSENSITIVITY Some allergens invoke delayed hypersensitivity, a T-cell-mediated immune response, rather than an immediate, B cell–IgE antibody response. Among these allergens are poison ivy toxin and certain chemicals to which the skin is frequently exposed, such as cosmetics and household cleaning agents. Most commonly, the response is characterized by a delayed skin eruption that reaches its peak intensity 1 to 3 days after contact with an allergen to which the T-cell system has previously been sensitized. To illustrate, poison ivy toxin does not harm the skin on contact, but it activates T cells specific for the toxin, including formation of a memory component. On subsequent exposure to the toxin, activated T cells diffuse into the skin within a day or two, combining with the poison ivy toxin that is present. The resulting interaction gives rise to the tissue damage and discomfort typical of the condition. The best relief is obtained from application of anti-inflammatory preparations, such as those containing cortisol derivatives.

Table 12-5 summarizes the distinctions between immediate and delayed hypersensitivities. This completes our discussion of the internal immune defense system. We now turn to external defenses that thwart entry of foreign invaders as a first line of defense.

TABLE 12-5 Immediate versus Delayed Hypersensitivity Reactions

Characteristic	Immediate Hypersensitivity Reaction	Delayed Hypersensitivity Reaction
Time of onset of symptoms after exposure to the allergen	Within 20 minutes	Within 1 to 3 days
Type of immune response	Antibody-mediated immunity against the allergen	Cell-mediated immunity against the allergen
Immune effectors involved	B cells, IgE antibodies, mast cells, basophils, histamine, slow-reactive substance of anaphylaxis, and eosinophil chemotactic factor	T cells
Allergies commonly involved	Hay fever, asthma, hives, and (in extreme cases) anaphylactic shock	Contact allergies, such as allergies to poison ivy, cosmetics, and household cleaning agents

Check Your Understanding 12.6

1. Compare the type of immune response and immune effectors involved in immediate hypersensitivity and delayed hypersensitivity.
2. Discuss how the mechanism of action of IgE antibodies differs from that of IgG antibodies.

12.7 External Defenses

The body's defenses against foreign microbes are not limited to the intricate, interrelated immune mechanisms that destroy microorganisms that have actually invaded the body. In addition to the internal immune defense system, the body is equipped with external defense mechanisms designed to prevent microbial penetration wherever body tissues are exposed to the external environment. All of our epithelial surfaces, namely the skin and the linings of the digestive tract, the urogenital (urinary and reproductive) tracts, and respiratory airways and lungs, are protected by antimicrobial peptides called **defensins**. Epithelial cells of these surfaces secrete defensins on attack by microbial pathogens, thereby killing the would-be invaders by disrupting their membranes.

The most obvious external defense is the **skin**, or **integument**, which covers the outside of the body (*integere* means "to cover").

The skin consists of an outer protective epidermis and an inner, connective tissue dermis.

The skin, which is the largest organ of the body, not only is a mechanical barrier between the external environment and the underlying tissues but is dynamically involved in defense mechanisms and other important functions as well. The skin in an average adult weighs 9 pounds and covers a surface area of 21 square feet. Its deeper layer contains an abundance of blood

vessels, which if laid end to end would extend more than 11 miles. The skin consists of two layers, an outer *epidermis* and an inner *dermis* (► Figure 12-25).

EPIDERMIS The **epidermis** consists of numerous layers of epithelial cells. On average, the epidermis replaces itself about every 2.5 months. The inner epidermal layers are composed of cube-shaped cells that are living and rapidly dividing, whereas the cells in the outer layers are dead and flattened. The epidermis has no direct blood supply. Its cells are nourished only by diffusion of nutrients from the rich vascular network in the underlying dermis. The newly forming cells in the inner layers constantly push the older cells closer to the surface and ever farther from their nutrient supply. This, coupled with the continuous subjection of the outer layers to pressure and "wear and tear," causes these older cells to die and become flattened. Epidermal cells are riveted tightly together by desmosomes (see p. 62), which interconnect with intracellular keratin filaments (see p. 53) to form a strong, cohesive covering. During maturation of a keratin-producing cell, keratin filaments progressively accumulate and cross-link with one another within the cytosol. As the outer cells die, this fibrous keratin core remains, forming flattened, hardened scales that provide a tough, protective **keratinized layer**. As the scales of the outermost keratinized layer slough or flake off through abrasion, they are continuously replaced by means of cell division in the deeper epidermal layers. The rate of cell division, and consequently the thickness of this keratinized layer, varies in different regions of the body. It is thickest in the areas where the skin is subjected to the most pressure, such as the bottom of the feet. The keratinized layer is airtight, fairly waterproof, and impervious to most substances. It resists anything passing in either direction between the body and the external environment. For example, it minimizes loss of water and other vital constituents from the body and prevents most foreign material from penetrating into the body.

 This protective layer's value in holding in body fluids becomes obvious after severe burns. Bacterial infections can occur in the unprotected underlying tissue, but even more serious are the systemic consequences of loss of body water and

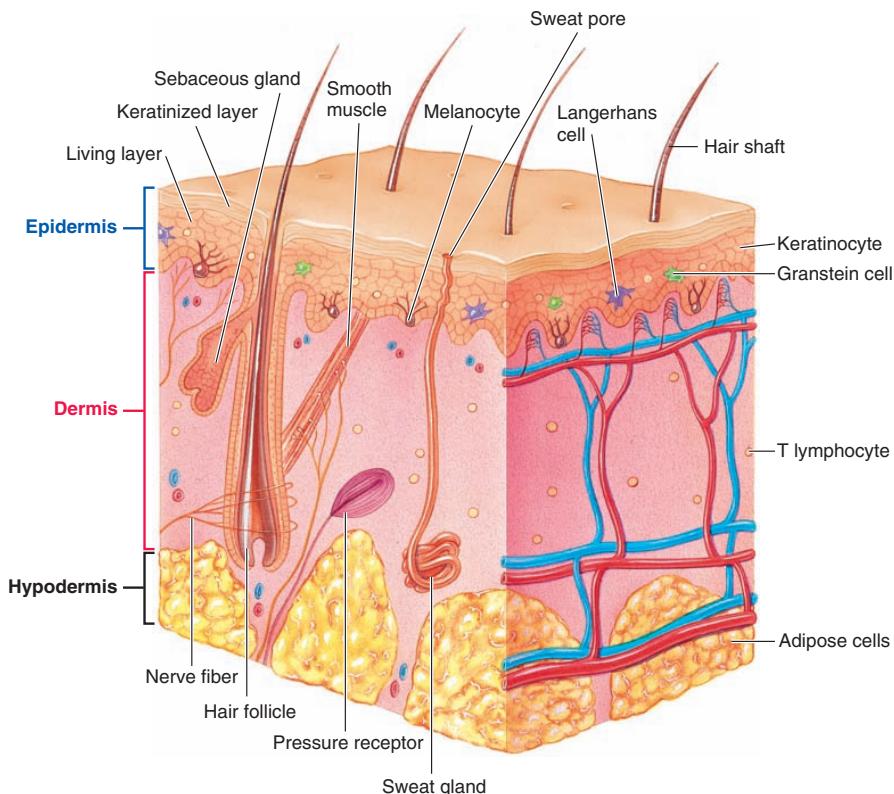


Figure 12-25 Anatomy of the skin. The skin consists of two layers, a keratinized outer epidermis and a richly vascularized inner connective tissue dermis. Special infoldings of the epidermis form the sweat glands, sebaceous glands, and hair follicles. The epidermis contains four types of cells: keratinocytes, melanocytes, Langerhans cells, and Granstein cells. The skin is anchored to underlying muscle or bone by the hypodermis, a loose, fat-containing layer of connective tissue

plasma proteins, which escape from the exposed, burned surface. The resulting circulatory disturbances can be life threatening.

Likewise, the skin barrier impedes passage into the body of most materials that come into contact with the body surface, including bacteria and toxic chemicals. In many instances, the skin modifies compounds that come into contact with it. For example, epidermal enzymes can convert many potential carcinogens into harmless compounds. Some materials, however, especially lipid-soluble substances, can penetrate intact skin through the lipid bilayers of the plasma membranes of the epidermal cells. Drugs that can be absorbed by the skin, such as nicotine or estrogen, are sometimes used in the form of a cutaneous “patch” impregnated with the drug.

DERMIS Under the epidermis is the **dermis**, a connective tissue layer that contains many elastin fibers (for stretch) and collagen fibers (for strength) and an abundance of blood vessels and specialized nerve endings. The dermal blood vessels not only supply both the dermis and the epidermis but also play a major role in temperature regulation. The caliber of these vessels, and hence the volume of blood flowing through them, is subject to control to vary the amount of heat exchange between these skin surface vessels and the external environment (see Chapter 17). Receptors

at the peripheral endings of afferent nerve fibers in the dermis detect pressure, temperature, pain, and other somatosensory input. Efferent nerve endings in the dermis control blood vessel caliber, hair erection, and secretion by the skin’s exocrine glands.

SKIN’S EXOCRINE GLANDS AND HAIR FOLLICLES

Special infoldings of the epidermis into the underlying dermis form the skin’s exocrine glands—the sweat glands and the sebaceous glands—as well as the hair follicles. **Sweat glands**, which are distributed over most of the body, release a dilute salt solution through small openings, the sweat pores, onto the skin surface (Figure 12-25). Evaporation of this sweat cools the skin and is important in regulating temperature.

The amount of sweat produced is subject to regulation and depends on the environmental temperature, the amount of heat-generating skeletal muscle activity, and various emotional factors (for example, a person often sweats when nervous). A special type of sweat

gland located in the axilla (armpit) and pubic region produces a protein-rich sweat that supports the growth of surface bacteria, which give rise to a characteristic odor. In contrast, most sweat, as well as the secretions from the sebaceous glands, contains chemicals that are generally highly toxic to bacteria.

The cells of the **sebaceous glands** produce **sebum**, an oily secretion released into adjacent hair follicles. From there sebum flows to the skin surface, oiling both the hairs and the outer keratinized layers of the skin, helping to waterproof them and prevent them from drying and cracking. Chapped hands or lips indicate insufficient protection by sebum. The sebaceous glands are particularly active during adolescence, causing the oily skin common among teenagers.

Each **hair follicle** is lined by special keratin-producing cells, which secrete keratin and other proteins that form the hair shaft. Hairs increase the sensitivity of the skin’s surface to tactile (touch) stimuli. In some other species, this function is more finely tuned. For example, the whiskers on a cat are exquisitely sensitive in this regard. An even more important role of hair in hairier species is heat conservation, but this function is not significant in us relatively hairless humans. Like hair, the **nails** are another special keratinized product derived from living epidermal structures, the nail beds.

HYPODERMIS The skin is anchored to the underlying tissue (muscle or bone) by the **hypodermis** (*hypo* means “below”), also known as **subcutaneous tissue** (*sub* means “under”; *cutaneous* means “skin”), a loose layer of connective tissue. Most fat cells are housed within the hypodermis. These fat deposits throughout the body are collectively referred to as **adipose tissue**.

Specialized cells in the epidermis produce keratin and melanin and participate in immune defense.

The epidermis contains four distinct resident cell types—*melanocytes*, *keratinocytes*, *Langerhans cells*, and *Granstein cells*—plus transient T lymphocytes that are scattered throughout the epidermis and dermis. Each of these resident cell types performs specialized functions.

MELANOCYTES Melanocytes produce the pigment **melanin**, which they disperse to surrounding skin cells. The amount and type of melanin, which can vary among black, brown, yellow, and red pigments, are responsible for the shades of skin color of the various races. Fair-skinned people have about the same number of melanocytes as dark-skinned people; the difference in skin color depends on the amount of melanin produced by each melanocyte. Melanin is produced through complex biochemical pathways in which the melanocyte enzyme *tyrosinase* plays a key role. Most people, regardless of skin color, have enough tyrosinase that, if fully functional, could result in enough melanin to make their skin very black. In those with lighter skin, however, two genetic factors prevent this melanocyte enzyme from functioning at full capacity: (1) much of the tyrosinase produced is in an inactive form, and (2) various inhibitors that block tyrosinase action are produced. As a result, less melanin is produced.

In addition to hereditary determination of melanin content, the amount of this pigment can be increased transiently in response to exposure to ultraviolet (UV) light rays from the sun. On exposure to UV light, keratinocytes secrete **α -melanocyte stimulating hormone** (**α -MSH**), which acts as a paracrine on neighboring melanocytes to darken the skin. This additional melanin, the outward appearance of which constitutes a “tan,” performs the protective function of absorbing harmful UV rays.

KERATINOCYTES The most abundant epidermal cells are the **keratinocytes**, which, as the name implies, are specialists in keratin production. As they die, they form the outer protective keratinized layer. They also generate hair and nails. Furthermore, keratinocytes are important immunologically. They secrete IL-1 (a product also secreted by macrophages), which influences the maturation of T cells that tend to localize in the skin. Interestingly, the epithelial cells of the thymus bear anatomic, molecular, and functional similarities to those of the skin. Apparently, some post-thymic steps in T-cell maturation take place in the skin under keratinocyte guidance.

OTHER IMMUNE CELLS OF THE SKIN The two other epidermal cell types also play a role in immunity. **Langerhans**

cells, which migrate to the skin from the bone marrow, are dendritic cells that serve as antigen-presenting cells. Thus, the skin not only is a mechanical barrier but actually alerts lymphocytes if the barrier is breached by invading microorganisms. Langerhans cells present antigen to helper T cells, facilitating their responsiveness to skin-associated antigens. In contrast, **Granstein cells** act as a “brake” on skin-activated immune responses. They are antigen-presenting cells to skin-associated T_{reg}s, thus exerting an immune suppressor effect. Granstein cells are the most recently discovered and least understood of the skin’s immune cells. Significantly, Langerhans cells are more susceptible to damage by UV radiation than Granstein cells are. Losing Langerhans cells as a result of exposure to UV radiation can detrimentally lead to a predominant suppressor signal rather than the normally dominant helper signal, leaving the skin more vulnerable to microbial invasion and cancer cells.

The various epidermal components of the immune system are collectively termed **skin-associated lymphoid tissue**, or **SALT**. This is appropriate because the skin serves as a major interface with the external environment.

VITAMIN D SYNTHESIS BY THE SKIN The epidermis also synthesizes vitamin D in the presence of sunlight. The cell type that produces vitamin D is undetermined. Vitamin D, which is derived from a precursor molecule closely related to cholesterol, promotes the absorption of Ca²⁺ from the digestive tract into the blood (Chapter 16). Dietary supplements of vitamin D are usually required because typically the skin is not exposed to sufficient sunlight to produce adequate amounts of this essential chemical.

Protective measures within body cavities discourage pathogen invasion into the body.

The human body’s defense system must guard against entry of potential pathogens not only through the outer surface of the body but also through the internal cavities that communicate directly with the external environment—namely, the digestive system, the urogenital system, and the respiratory system. These systems use various tactics to destroy microorganisms entering through these routes.

DEFENSES OF THE DIGESTIVE SYSTEM Saliva secreted into the mouth at the entrance of the digestive system contains an enzyme that lyses certain ingested bacteria. “Friendly” bacteria that live on the back of the tongue convert food-derived nitrate into nitrite, which is swallowed. Acidification of nitrite on reaching the highly acidic stomach generates nitric oxide, which is toxic to a variety of microorganisms. Furthermore, many of the surviving bacteria that are swallowed are killed directly by the strongly acidic gastric juice in the stomach. Farther down the tract, the intestinal lining is endowed with gut-associated lymphoid tissue. These defensive mechanisms are not 100% effective, however. Some bacteria do manage to survive and reach the large intestine (the last portion of the digestive tract), where they continue to flourish. Surprisingly, this normal microbial population provides a natural barrier against infection within the lower intestine. These harmless resident

microbes competitively suppress the growth of potential pathogens that have managed to escape the antimicrobial measures of earlier parts of the digestive tract.

 Occasionally, orally administered antibiotic therapy against an infection elsewhere within the body may induce an intestinal infection. By knocking out some normal intestinal bacteria, an antibiotic may permit an antibiotic-resistant pathogenic species to overgrow in the intestine.

DEFENSES OF THE UROGENITAL SYSTEM Within the urogenital system, would-be invaders encounter hostile conditions in the acidic urine and acidic vaginal secretions. The urogenital organs also produce a sticky mucus, which, like flypaper, entraps small invading particles. Subsequently, the particles are either engulfed by phagocytes or are swept out as the organ empties (for example, they are flushed out with urine flow).

DEFENSES OF THE RESPIRATORY SYSTEM The respiratory system is likewise equipped with several important defense mechanisms against inhaled particulate matter. The respiratory system is the largest surface of the body that comes into direct contact with the increasingly polluted external environment. The surface area of the respiratory system exposed to the air is 30 times that of the skin. Larger airborne particles are filtered out of the inhaled air by hairs at the entrance of the nasal passages. Lymphoid tissues, the *tonsils* and *adenoids*, provide immunological protection against inhaled pathogens near the beginning of the respiratory system. Farther down in the respiratory airways, millions of tiny hairlike projections known as *cilia* constantly beat in an outward direction (see p. 48). The respiratory airways are coated with a layer of thick, sticky mucus secreted by epithelial cells within the airway lining. This mucus sheet, laden with any inspired particulate debris (such as dust) that adheres to it, is constantly moved upward to the throat by ciliary action. This moving “staircase” of mucus is known as the **mucus escalator**. The dirty mucus is either expectorated (spit out) or, in most cases, is swallowed without the person even being aware of it; any indigestible foreign particulate matter is later eliminated in the feces. Besides keeping the lungs clean, this mechanism is an important defense against bacterial infection because many bacteria enter the body on dust particles. Also contributing to defense against respiratory infections are antibodies secreted in the mucus. In addition, an abundance of phagocytic specialists called **alveolar macrophages** scavenge within the air sacs (alveoli) of the lungs. Further respiratory defenses include coughs and sneezes. These commonly experienced reflex mechanisms involve forceful outward expulsion of material in an attempt to remove irritants from the trachea (*coughs*) or nose (*sneezes*). A sneeze can propel air and particles from the respiratory airways up to 30 feet away at rates over 90 miles per hour.

 Cigarette smoking suppresses these normal respiratory defenses. The smoke from a single cigarette can paralyze the cilia for several hours, with repeated exposure eventually leading to ciliary destruction. Failure of ciliary activity to sweep out a constant stream of particulate-laden mucus enables inhaled carcinogens to remain in contact with the respiratory airways for prolonged periods. Furthermore, cigarette smoke

incapacitates alveolar macrophages. In addition, noxious agents in tobacco smoke irritate the mucous linings of the respiratory tract, resulting in excess mucus production, which may partially obstruct the airways. “Smoker’s cough” is an attempt to dislodge this excess stationary mucus. These and other direct toxic effects on lung tissue lead to the increased incidence of lung cancer and chronic respiratory diseases associated with cigarette smoking. Air pollutants include some of the same substances found in cigarette smoke and can similarly affect the respiratory system.

We examine the respiratory system in greater detail in the next chapter.

Check Your Understanding 12.7

1. Describe the epidermis, dermis, and hypodermis.
2. List and state the functions of the four resident cell types in the skin.

Homeostasis: Chapter in Perspective

 We could not survive beyond early infancy were it not for the body’s defense mechanisms. These mechanisms resist and eliminate potentially harmful foreign agents with which we continuously come into contact in our hostile external environment and also destroy abnormal cells that often arise within the body. Homeostasis can be optimally maintained, and thus life sustained, only if the body cells are not physically injured or functionally disrupted by pathogenic microorganisms or are not replaced by abnormally functioning cells, such as traumatized cells or cancer cells. The immune defense system—a complex, multifaceted, interactive network of leukocytes, their secretory products, and plasma proteins—contributes indirectly to homeostasis by keeping other cells alive so that they can perform their specialized activities to maintain a stable internal environment. The immune system protects the other healthy cells from foreign agents that have gained entrance to the body, clears away dead and injured cells to pave the way for replacement with healthy new cells, and eliminates newly arisen cancer cells.

The skin contributes indirectly to homeostasis by serving as a protective barrier between the external environment and the rest of the body cells. It helps prevent harmful foreign agents such as pathogens and toxic chemicals from entering the body and helps prevent the loss of precious internal fluids from the body. The skin also contributes directly to homeostasis by helping maintain body temperature by means of the sweat glands and adjustments in skin blood flow. The amount of heat carried to the body surface for dissipation to the ex-

ternal environment is determined by the volume of warmed blood flowing through the skin.

Other systems that have internal cavities in contact with the external environment, such as the digestive, urogenital,

and respiratory systems, also have defense capabilities to prevent harmful external agents from entering the body through these avenues.

REVIEW EXERCISES

Answers begin on p. A-33.

Objective Questions

1. The complement system can be activated only by antibodies. (*True or false?*)
2. Specific adaptive immune responses are accomplished by neutrophils. (*True or false?*)
3. Damaged tissue is always replaced by scar tissue. (*True or false?*)
4. Active immunity against a particular disease can be acquired only by actually having the disease. (*True or false?*)
5. A secondary response has a more rapid onset, is more potent, and has a longer duration than a primary response. (*True or false?*)
6. _____ are receptors on the plasma membrane of phagocytes that recognize and bind with telltale molecular patterns present on the surface of microorganisms but absent from human cells.
7. The complement system's _____ forms a doughnut-shaped complex that embeds in a microbial surface membrane, causing osmotic lysis of the victim cell.
8. _____ is a collection of phagocytic cells, necrotic tissue, and bacteria.
9. _____ is the localized response to microbial invasion or tissue injury that is accompanied by swelling, heat, redness, and pain.
10. A chemical that enhances phagocytosis by serving as a link between a microbe and the phagocytic cell is known as a(n) _____.
11. _____, collectively, are all the chemical messengers other than antibodies secreted by lymphocytes.
12. Which of the following statements concerning leukocytes is/are *incorrect*?
 - a. Monocytes are transformed into macrophages.
 - b. T lymphocytes are transformed into plasma cells that secrete antibodies.
 - c. Neutrophils are highly mobile phagocytic specialists.
 - d. Basophils release histamine.
 - e. Lymphocytes arise in large part from lymphoid tissues.
13. Match the following:

1. a family of proteins that nonspecifically defend against viral infection	(a) complement system
(b) natural killer (NK) cells	(b) natural killer (NK) cells
2. a response to tissue injury in which neutrophils and macrophages play a major role	(c) interferon
(d) inflammation	(d) inflammation
3. a group of plasma proteins that, when activated, bring about destruction of foreign cells by attacking their plasma membranes	
4. lymphocyte-like entities that spontaneously lyse tumor cells and virus-infected host cells
14. Using the answer code on the right, indicate whether the numbered characteristics of the adaptive immune system apply to antibody-mediated immunity or cell-mediated immunity (or both):

1. involves secretion of antibodies	(a) antibody-mediated immunity																
2. mediated by B cells	(b) cell-mediated immunity																
3. mediated by T cells	(c) both antibody-mediated and cell-mediated immunity																
4. accomplished by thymus-educated lymphocytes																	
5. triggered by the binding of specific antigens to complementary lymphocyte receptors																	
6. involves formation of memory cells in response to initial exposure to an antigen																	
7. primarily aimed against virus-infected host cells																	
8. protects primarily against bacterial invaders																	
9. directly destroys targeted cells																	
10. involved in rejection of transplanted tissue																	
11. requires binding of a lymphocyte to a free extracellular antigen																	
12. requires dual binding of a lymphocyte with both foreign antigen and self-antigens present on the surface of a host cell																	
15. Using the answer code on the right, indicate whether the numbered characteristics apply to the epidermis or dermis: <table border="0" style="width: 100%;"><tr><td style="width: 50%;">1. is the inner layer of skin</td><td style="width: 50%;">(a) epidermis</td></tr><tr><td>2. has layers of epithelial cells that are dead and flattened</td><td>(b) dermis</td></tr><tr><td>3. has no direct blood supply</td><td></td></tr><tr><td>4. contains sensory nerve endings</td><td></td></tr><tr><td>5. contains keratinocytes</td><td></td></tr><tr><td>6. contains melanocytes</td><td></td></tr><tr><td>7. contains rapidly dividing cells</td><td></td></tr><tr><td>8. is mostly connective tissue</td><td></td></tr></table>	1. is the inner layer of skin	(a) epidermis	2. has layers of epithelial cells that are dead and flattened	(b) dermis	3. has no direct blood supply		4. contains sensory nerve endings		5. contains keratinocytes		6. contains melanocytes		7. contains rapidly dividing cells		8. is mostly connective tissue		
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6. contains melanocytes																	
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8. is mostly connective tissue																	

Essay Questions

(Answers at www.cengagebrain.com)

1. Distinguish between bacteria and viruses.
2. Summarize the functions of each of the lymphoid tissues.
3. Distinguish between innate and adaptive immune responses.
4. Compare the life histories of B cells and T cells.
5. Describe the structure of an antibody. List and describe the five subclasses of immunoglobulins.
6. In what ways do antibodies exert their effect?

7. Describe the clonal selection theory.
8. Compare the functions of B cells and T cells. What are the roles of the three types of T cells?
9. Summarize the functions of macrophages in immune defense.
10. What mechanisms are involved in tolerance?
11. What is the importance of class I and class II MHC glycoproteins?
12. Describe the factors that contribute to immune surveillance against cancer cells.
13. Distinguish among immunodeficiency disease, autoimmune disease, immune complex disease, immediate hypersensitivity, and delayed hypersensitivity.
14. What are the immune functions of the skin?

Quantitative Exercises

- As a result of the innate immune response to an infection—for example, from a cut on the skin—capillary walls near the site of infection become very permeable to plasma proteins that normally remain in the blood. These proteins diffuse into the interstitial fluid, raising the interstitial fluid–colloid osmotic pressure. This increased colloid osmotic pressure

causes fluid to leave the circulation and accumulate in the tissue, forming a welt, or wheal. This process is referred to as the *wheal response*. The wheal response is mediated in part by histamine secreted from mast cells in the area of infection. The histamine binds to receptors, called *H-1 receptors*, on capillary endothelial cells. The histamine signal is transduced via the Ca^{2+} second-messenger pathway involving phospholipase C (see p. 125). In response to this signal, the capillary endothelial cells contract (via internal actin–myosin interaction), which causes a widening of the intercellular gaps (pores) between the capillary endothelial cells (see p. 364). In addition, substance P (see p. 194) also contributes to pore widening. Plasma proteins can pass through these widened pores and leave the capillaries. Looking at Figure 10-22, p. 367, compare the magnitude of the wheal response (that is, the extent of localized edema) if P_{IF} were raised (a) from 0 mm Hg to 5 mm Hg and (b) from 0 mm Hg to 10 mm Hg. In both cases, compare the net exchange pressure (NEP) at the arteriolar end of the capillary, the venular end of the capillary, and the average NEP. (Assume the other forces acting across the capillary wall remain unchanged.)

POINTS TO PONDER

- Compare the defense mechanisms that come into play in response to bacterial and viral pneumonia.
- Nearly 30 years have passed since the first cases of AIDS were reported in the United States and millions of research dollars have been spent studying this disease. Much has been learned, and drugs have been developed that delay or manage the condition, but no AIDS vaccine has been approved despite many unsuccessful attempts. Why does the frequent mutation of HIV (the AIDS virus) make it difficult to develop a vaccine against this virus?
- What impact would failure of the thymus to develop embryonically have on the immune system after birth?
- Medical researchers are currently working on ways to “teach” the immune system to view foreign tissue as “self.” What useful clinical application will the technique have?
- When someone looks at you, are the cells of your body that person is viewing dead or alive?

CLINICAL CONSIDERATION

Linda P. is allergic to molds and dust mites. She takes allergy medication as needed to keep her symptoms under control, but in the hopes of ridding herself of the troublesome allergies, she has been taking allergy (desensitization) shots. Allergy shots consist of weekly injections of minute, gradually increasing doses of the offending allergens. How can deliberately injecting the offending agent lead to a reduction in allergic response to

the allergen? The leading theory regarding the mechanism of action of allergy shots is that the immune response to the allergen is gradually shifted from production of IgE antibodies to production of IgG antibodies against this antigen. How would this switch lead to a reduction in allergic symptoms on environmental exposure to higher doses of the antigen?



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CHAPTER 12

Study Card

12.1 | Immune System: Targets, Effectors, Components (pp. 415–418)

- Foreign invaders and newly arisen mutant cells are immediately confronted with multiple interrelated defense mechanisms aimed at destroying and eliminating anything that is not part of the normal self. These mechanisms, collectively referred to as immunity, include both innate and adaptive immune responses. Innate immune responses are nonspecific responses that nonselectively defend against foreign material even on initial exposure to it. Adaptive immune responses are specific responses that selectively target particular invaders for which the body has been specially prepared after a prior exposure.
 - The most common invaders are bacteria and viruses. Bacteria are self-sustaining, single-celled organisms that produce disease by virtue of the destructive chemicals they release. Viruses are protein-coated nucleic acid particles that invade host cells and take over the cellular metabolic machinery for their own survival to the detriment of the host cell.
 - Leukocytes and their derivatives are the major effector cells of the immune system and are reinforced by a number of different plasma proteins. Leukocytes include neutrophils, eosinophils, basophils, monocytes, and lymphocytes.
 - Immune cells also clean up cellular debris, preparing the way for tissue repair.

12.2 | Innate Immunity (pp. 418–425)

- Innate immune responses include inflammation, interferon, natural killer (NK) cells, and the complement system.
 - Inflammation is a nonspecific response to foreign invasion or tissue damage mediated largely by the professional phagocytes (neutrophils and monocytes-turned-macrophages). The phagocytic cells destroy foreign and damaged cells both by phagocytosis and by release of lethal chemicals. (Review Figures 12-2 and 12-3 and chapter opener.) Phagocytic secretions also augment inflammation, induce systemic manifestations such as fever, and enhance adaptive immune responses.
 - Histamine-induced vasodilation and increased permeability of local capillaries at the site of invasion or injury permit enhanced delivery of more phagocytic leukocytes and inactive plasma protein precursors crucial to defense, such as complement components. These vascular changes also largely produce the observable local manifestations of inflammation—swelling, redness, heat, and pain. (Review Figure 12-3.)
 - Interferon is nonspecifically released by virus-infected cells and transiently inhibits viral multiplication in other cells to which it binds. (Review Figure 12-5.)
 - NK cells nonspecifically lyse and destroy virus-infected cells and cancer cells on first exposure to them.
 - On being activated by microbes themselves at the site of invasion or by antibodies produced against the microbes, the com-

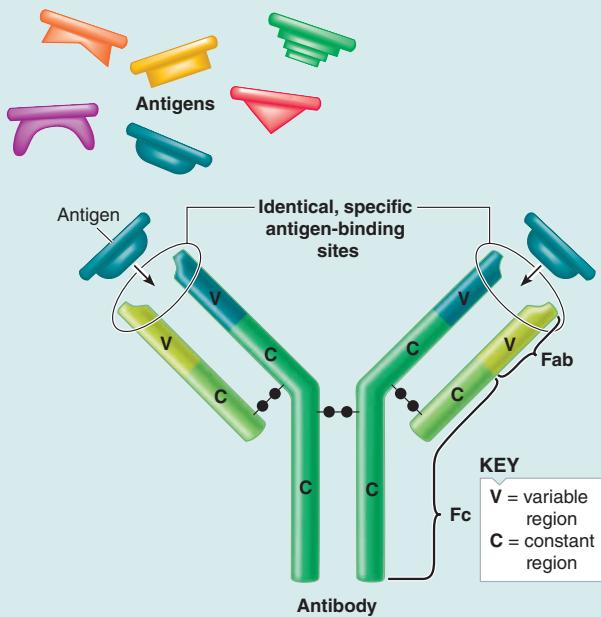
plement system directly destroys the foreign invaders by lysing their membranes and also augments other aspects of the inflammatory process, such as by acting as opsonins that enhance phagocytosis. The complement system lyses the targeted cells by forming a hole-punching membrane attack complex that inserts into the victim cell's membrane, leading to osmotic rupture of the cell. (Review Figures 12-4 and 12-6.)

12.3 | Adaptive Immunity: General Concepts (pp. 425–427)

- Not only is the adaptive immune system able to recognize foreign molecules as different from self-molecules—so that destructive immune reactions are not unleashed against the body itself—but it can also distinguish between millions of different foreign molecules. Lymphocytes, the effector cells of adaptive immunity, are each uniquely equipped with surface membrane receptors that can bind with only one specific complex foreign molecule, known as an antigen.
 - The two classes of adaptive immune responses are antibody-mediated immunity accomplished by plasma cells derived from B lymphocytes (B cells), and cell-mediated immunity accomplished by T lymphocytes (T cells). (Review Table 12-4, p. 445.)
 - B cells develop from a lineage of lymphocytes that originally matured within the bone marrow. The T-cell lineage comes from lymphocytes that migrated from the bone marrow to the thymus to complete their maturation. New B and T cells arise from lymphocyte colonies in lymphoid tissues. (Review Figures 12-1 and 12-7 and Table 12-1.)

12.4 | B Lymphocytes: Antibody-Mediated Immunity (pp. 427–433)

- Each B cell recognizes specific free extracellular antigen, such as that found on the surface of bacteria.
 - After being activated by binding of its receptor (a B-cell receptor, or BCR) with its specific antigen, a B cell rapidly proliferates, producing a clone of its own kind that can specifically wage battle against the invader. Most lymphocytes in the expanded B-cell clone become antibody-secreting plasma cells that participate in the primary response against the invader. Some of the new lymphocytes do not participate in the attack but become memory cells that lie in wait, ready to launch a swifter and more forceful secondary response should the same foreigner ever invade the body again. (Review Figures 12-8, 12-9, 12-12, and 12-13.)
 - Antibodies are Y-shaped molecules. The antigen-binding sites on the tips of each arm determine with what specific antigen the antibody can bind. Properties of the antibody's tail portion determine what the antibody does once it binds with antigen. There are five subclasses of antibodies, depending on differences in the biological activity of their tail portion: IgM, IgG, IgE, IgA, and IgD immunoglobulins. (Review Figure 12-10.)



■ Antibodies do not directly destroy antigenic material. Instead, they exert their protective effect by physically hindering antigens through neutralization or agglutination or by intensifying lethal innate immune responses already called into play by the foreign invasion. Antibodies activate the complement system, enhance phagocytosis, and stimulate NK cells. (Review Figures 12-11 and Table 12-3, p. 441.)

12.5 | T Lymphocytes: Cell-Mediated Immunity (pp. 433–446)

- T cells accomplish cell-mediated immunity by being in direct contact with their targets and by releasing cytokines, which are chemicals other than antibodies released by leukocytes.
- There are three types of T cells: cytotoxic, helper, and regulatory T cells.
- The targets of cytotoxic (CD8+) T cells are virally invaded cells and cancer cells, which they destroy by releasing perforin molecules that form a lethal hole-punching complex that inserts into the membrane of the victim cell or by releasing granzymes that trigger the victim cell to undergo apoptosis. (Review Figures 12-14 and 12-15 and Table 12-2.)
- Helper (CD4+) T cells bind with other immune cells and release cytokines that augment the activity of these other cells. B cells cannot convert to plasma cells and produce antibodies in response to T-dependent antigen without the help of helper cells. (Review Figure 12-20.)
- Regulatory (CD4+CD25+) cells (T_{reg}) secrete cytokines that suppress other immune cells, putting the brake on immune responses in check-and-balance fashion.
- Like B cells, T cells bear receptors (T-cell receptors or TCRs) that are antigen specific (Review Figure 12-8), undergo clonal selection, exert primary and secondary responses, and form memory pools for long-lasting immunity against targets to which they have already been exposed.
- Helper T cells can recognize and bind with antigen only when it has been processed and presented to them by antigen-

presenting cells (APCs), such as macrophages and dendritic cells. (Review Figures 12-17 and 12-18.)

■ Lymphocytes produced by chance that can attack the body's own cells are eliminated or suppressed so that they are prevented from functioning. In this way, the body is able to "tolerate" (not attack) its own antigens.

■ B and T cells have different targets because their requirements for antigen recognition differ. B cells recognize freely circulating antigen, such as bacteria, that can lead to antigen destruction at long distances via antibodies. T cells, in contrast, have a dual binding requirement of foreign antigen in association with self-antigens on the surface of one of the body's own cells. (Review Figures 12-19 and 12-20.)

■ The self-antigens on cell surfaces are class I or class II MHC molecules, which are unique for each individual. Cytotoxic T cells can bind only with virus-infected host cells or cancer cells, which always bear class I MHC self-antigen in association with foreign or abnormal antigen. Helper T cells can bind only with APCs and B cells that bear the class II MHC self-marker in association with foreign antigen. The APCs activate helper T cells, and helper T cells activate B cells. Thus, such differential binding ensures that the appropriate specific immune response ensues. (Review Figures 12-19 and 12-20.)

■ In the process of immune surveillance, natural killer cells, cytotoxic T cells, macrophages, and the interferon they collectively secrete normally eradicate newly arisen cancer cells before they have a chance to spread. (Review Figure 12-22.)

12.6 | Immune Diseases (pp. 446–450)

■ Immune diseases are of two types: immunodeficiency diseases (insufficient immune responses) or inappropriate immune attacks (excessive or mistargeted immune responses).

■ Inappropriate attacks include autoimmune diseases, immune complex diseases, and allergies (hypersensitivities), of which there are two types: (1) Immediate hypersensitivities involving the production of IgE antibodies by B cells that trigger release of histamine from mast cells and basophils to bring about a swift response to the allergen, and (2) delayed hypersensitivities involving a more slowly responding cell-mediated, symptom-producing response by T cells against the allergen. (Review Figures 12-23 and 12-24 and Table 12-5.)

12.7 | External Defenses (pp. 450–453)

■ The body surfaces exposed to the outside environment—both the outer covering of skin and the linings of internal cavities that communicate with the external environment—serve not only as mechanical barriers to deter would-be pathogenic invaders but also play an active role in thwarting entry of bacteria and other unwanted materials.

■ The skin consists of two layers: an outer keratinized epidermis and an inner vascularized, connective tissue dermis. The epidermis contains pigment-producing melanocytes, keratin-producing keratinocytes, immune-enhancing Langerhans cells, and immune-suppressive Granstein cells. (Review Figure 12-25.)

■ The other main routes by which potential pathogens enter the body are the digestive system, the urogenital system, and the respiratory system, which are all defended by various antimicrobial strategies.